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Isatin halogen-derivatives redox behaviour

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ABSTRACT

Isatin halogen-derivatives like other isatin derivatives have several pharmacoterapeutic applications, such as antibacterial, antitubercular, and anticancer activities. The electrochemical behaviour, at a glassy carbon electrode, of some mono- and di- fluoro, chloro, bromo and iodo isatin derivatives, by cyclic, square wave and differential pulse voltammetry, over a wide pH range, was investigated, and compared with isatin electrochemical behaviour. The presence of one or two halogens in the benzene ring affected the oxidation processes. The oxidation mechanism of isatin monohalogen-derivatives, with only one halogen at the position C5 or C7, was an irreversible, pH-dependent, adsorption-controlled process, and occurred in three consecutive charge transfer reactions, first on the benzene ring with the production of one hydroxyl group attached to the ring, and the electroactive oxidation product formed was oxidized to *para*- and/or *ortho*-quinone derivatives and polymeric products. The isatin dihalogen-derivatives oxidation was also irreversible, in two consecutive charge transfer reactions, with the formation of polymeric products, and occurred at more positive potentials. The reduction mechanism of isatin halogen-derivatives was a pH-dependent two consecutive charge transfer reactions. The first process was the reversible reduction of the carbon-halogen bond and the second the irreversible cleavage of the carbonyl group at the position C3 in the heterocyclic ring. The halogens substituents in the isatin benzene ring gave rise to different redox processes, depending on the number and halogen position.

1. Introduction

Isatin (1*H*-indole-2,3-dione) (ISA), one of the most important derivatives of indole, is an endogenous compound identified in many organisms, present in mammalian tissues and body fluids, and also as a natural product of plants, for example genus Isatis, in *Calanthe discolour*, Lindl, and in *Couroupita guianensis*, Aubl [1–3].

Isatin is a very important molecule due to its broad range of biological and pharmacological properties, and also because it is a synthetically versatile substrate. Isatin and its derivatives are extensively used as important raw materials for designing potential bioactive agents [3–5]. Recently the study of isatin derivatives have been shown to demonstrate antiprotozoal, antibacterial, antifungal, antiviral, *anti*-HIV, anticonvulsant, antitumoral, anti-inflammatory, antihelminthic activities, to influence neurodegenerative diseases, and to participate in metabolism [3,6–8].

Isatin halogen-derivatives have also been reported to exhibit several pharmacoterapeutic activities, such as antibacterial, antitubercular, anticancer and antineoplastic activities [9–20].

Isatin fluoro-derivatives are used in the synthesis of new compounds that may belong to a class of chemotherapeutic agents for the treatment of various bacterial infections, act by inhibiting DNA gyrase, the principal target in gram–negative bacteria, and also the topoisomerase IV, the principal target in gram-positive bacteria [13]. The isatin 5-fluoro-derivatives were also synthesized and the antitubercular activity was evaluated and some of the compounds presented complete inhibition against the *Mycobacterium tuberculosis* H37Rv strain [14]. In 2006, an isatin 5-fluoro-derivative (sunitinib) was approved by FDA for the treatment of gastrointestinal stromal tumours and advanced renal cell carcinoma [15–16].

Isatin bromo-derivatives have been shown to exhibit anticancer activity [17–19]. The in vitro cytotoxic activities of isatin bromo-derivatives were determined against the human monocyte-like, histiocytic lymphoma cell line (U937), showing that the introduction of electron-withdrawing groups at positions C5, C6, and C7 significantly increased the anticancer activity when compared with isatin, the substitution at the 5-position being the most favourable [18]. The C5 substitution in the isatin ring has been associated with increased biological activity for a range of indole-based compounds [18]. Both chloro and bromo substituted isatin derivatives presented antifungal and antibacterial activity but the isatin 5-chloro-derivatives, when compared with the

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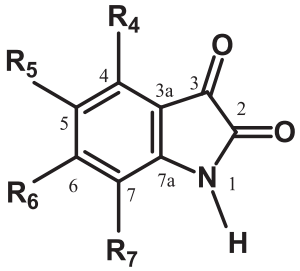
isatin 5-bromo-derivatives presented a better antibacterial activity [21]. The 5-chloro-isatin ketals, such as the dioxolane ketal of 5-chloro-isatin, have significant anticonvulsant and anxiolytic activities [22].

Electrochemical techniques have been widely used to study the structure, reactivity and mechanism of action of pharmaceutical and biological compounds. Also, other parameters can be evaluated using electrochemical data, such as stereochemistry, diffusion, solubility and metabolism. It should be considered that many physiological processes are depending on redox reactions, and it is easy to find complementary electrochemical and biological reactions, providing useful information on the mechanism of the compounds in living systems. These reactions are most often studied with electrochemical techniques, cyclic, square wave and differential pulse voltammetry, since they have high sensitivity and selectivity [23–27].

There are some studies concerning the redox behaviour of isatin and of its derivatives in aqueous and non-aqueous media, using voltammetry at glassy carbon or mercury electrodes [28–33]. Since isatin halogen-derivatives, in general, are having increasing applications in the synthesis of new molecules with pharmaceutical interest, the investigation of their in vitro redox behaviour is very important in order to predict the in vivo redox reactions.

The aim of the present study is focused on the redox behaviour of a series of eleven isatin mono- and dihalogen-derivatives, Scheme 1. The influence of the number and halogen atoms (F, Cl, Br and I), substituents in the isatin benzene ring, in the redox properties, for a wide range of solution conditions, using cyclic, square wave and differential pulse voltammetry at a glassy carbon electrode, was investigated and a redox mechanism proposed.



Compound	R_4	R_5	R_6	R_7
ISA	H	H	H	H
5-F-ISA	H	F	H	H
5-Cl-ISA	H	Cl	H	H
5-Br-ISA	H	Br	H	H
5-I-ISA	H	I	H	H
7-Cl-ISA	H	H	H	Cl
7-I-ISA	H	H	H	I
4,6-Br-ISA	Br	H	Br	H
5,7-diCl-ISA	H	Cl	H	Cl
5,7-diBr-ISA	H	Br	H	Br
5,7-F-Cl-ISA	H	F	H	Cl
5,7-Br-Cl-ISA	H	Br	H	Cl

Scheme 1. Chemical structures of isatin and isatin halogen-derivatives.

2. Experimental

2.1. Materials and reagents

The isatin and all isatin halogen-derivatives were synthetized according to methods described in the literature [5,34–37], Scheme 1. Stock solutions of isatin and all isatin halogen-derivatives, with a concentration of 1 mM, in ethanol, were prepared and stored at 4 °C.

Supporting electrolyte solutions, with ionic strength $I = 0.1$ M, of different pH composition: pH 2.0 (HCl + KCl), pH 3.3 (HOAc + NaOAc), pH 4.5 (HOAc + NaOAc), pH 5.2 (HOAc + NaOAc), pH 5.9 (NaH_2PO_4 + Na_2HPO_4), pH 7.2 (NaH_2PO_4 + Na_2HPO_4), pH 8.0 (NaH_2PO_4 + Na_2HPO_4), pH 9.2 (NaOH + $Na_2B_2O_7$), pH 11.2 (NaOH + Na_2HPO_4), using analytical grade reagents and purified water from a Millipore Milli-Q system (conductivity ≤ 0.1 μS cm-1) according to the literature, were prepared [38].

Nitrogen saturated solutions were obtained by bubbling high purity N_2 for a minimum of 10 min in the solution, and continuing with a N_2 flow over the solution during the voltammetric experiments.

Microvolumes were measured using electronic pipettes (EP), EP-10 μM and EP-100 μM Plus Motorized (Rainin Instrument Co. Inc., Woburn, USA). The pH measurements were carried out with a Crison micropH 2001 pH-meter with an Ingold combined glass electrode.

All experiments were done at room temperature, $T = 298$ K (25 °C).

2.2. Voltammetric parameters and electrochemical cells

Voltammetric experiments were carried out using a μAutolab running with GPES 4.9 software, Metrohm/Autolab, Utrecht, The Netherlands. Measurements were carried out using a glassy carbon working electrode (GCE) (d = 1.5 mm), a Pt wire counter electrode, and an Ag/AgCl (3 M KCl) as reference electrode, in a 1 mL one-compartment electrochemical cell (eDAQ Europe). The experimental conditions for cyclic voltammetry (CV) were scan rate 100 mV s^{-1}, and for differential pulse (DP) voltammetry were: pulse amplitude 50 mV, pulse width 70 ms, and scan rate 5 mV s^{-1}. For square wave (SW) voltammetry the experimental conditions were frequency 25 Hz and potential increment 2 mV, corresponding to an effective scan rate of 50 mV s^{-1}.

The GCE was polished using diamond spray (particle size 1 μm, Kement, Kent, UK) before every electrochemical assay. After polishing, the electrode was rinsed thoroughly with Milli-Q water. Following this mechanical treatment, the GCE was placed in buffer supporting electrolyte and various DP voltammograms were recorded until a steady state baseline voltammogram was obtained. This procedure ensured very reproducible experimental results.

2.3. Acquisition and presentation of voltammetric data

All DP Voltammograms presented were baseline-corrected using the moving average application with a step window of 2 mV included in the GPES version 4.9 software. This mathematical treatment improved the visualization and identification of peaks over the baseline without introducing any artefact, although the peak current is in some cases reduced (<10%) relative to that of the untreated curve. Nevertheless, this mathematical treatment of the original DP voltammograms was used in the presentation of all experimental DP voltammograms for a better and clearer identification of the peaks.

3. Results and discussion

Initial studies concerning the voltammetric behaviour of eleven isatin halogen-derivatives, Scheme 1, with substituents at C4, C5, C6 or C7 positions, were carried out in 0.1 M phosphate buffer pH = 7.0, N_2 saturated solutions, in 200 μM isatin halogen-derivatives, by CV, scan rate 100 mV s^{-1}, at a GCE. During the voltammetric measurement