



# Electrochemical oxidation mechanism of procarbazine at glassy carbon electrode



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## ABSTRACT

A voltammetric study of the redox behavior of procarbazine (PCZ), one of the most used chemotherapy agents to face Hodgkin's lymphoma, was carried out to investigate its oxidation at glassy carbon electrode (GCE). Essays of cyclic, differential pulse and square-wave voltammetries, on a large pH interval, revealed the electrochemical oxidation behavior of PCZ as an irreversible adsorption-controlled oxidation process, occurring in four consecutive charge transfer steps. The first, second and third steps are pH-dependent and occur with the transfer of one electron and one proton, leading to the formation of an electroactive product in acid media, while the last one is pH-independent, involving the transfer of one electron. A reaction mechanism for the electrochemical oxidation of PCZ is proposed, where, in the first and second step the oxidation occurs on the hydrazine group, followed by isomerization and, after hydrolysis, conversion to benzaldehyde-procarbazine. The third and fourth steps are associated with the oxidation of the benzaldehyde-procarbazine with the production of the N-isopropylterephthalic acid.

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## 1. Introduction

Procarbazine [N-isopropyl- $\alpha$ -(2-methylhydrazino)-p-toluamide hydrochloride, PCZ, Matulane, Nathulane, Natulanar], a chemotherapeutic hydrazine, [Scheme 1](#), is one of the most used chemotherapy agents to face Hodgkin's lymphoma, being applied also to non-Hodgkin's lymphomas and various other forms of cancer [1]. PCZ induces pulmonary tumors, leukemia, mammary adenocarcinoma and nasal tumor in animals [2–4]. The MOPP chemotherapy (mustargen, oncovin, procarbazine and prednisone) was found to induce lung tumor and leukemia in humans [2].

The mechanism of action of PCZ is not yet fully understood, but there is some evidence suggesting that several enzymes and certain transition metal ions, as horseradish peroxidase, prostaglandin synthetase, cytochrome P450 and copper (II), catalyze oxidation of PCZ, leading to the formation of toxic derivatives, such as azo derivatives, the hydrazine, the aldehyde and carbon-centered and oxygen free radicals, that in contact with DNA can cause alkylation and/or oxidative damage [1–6].

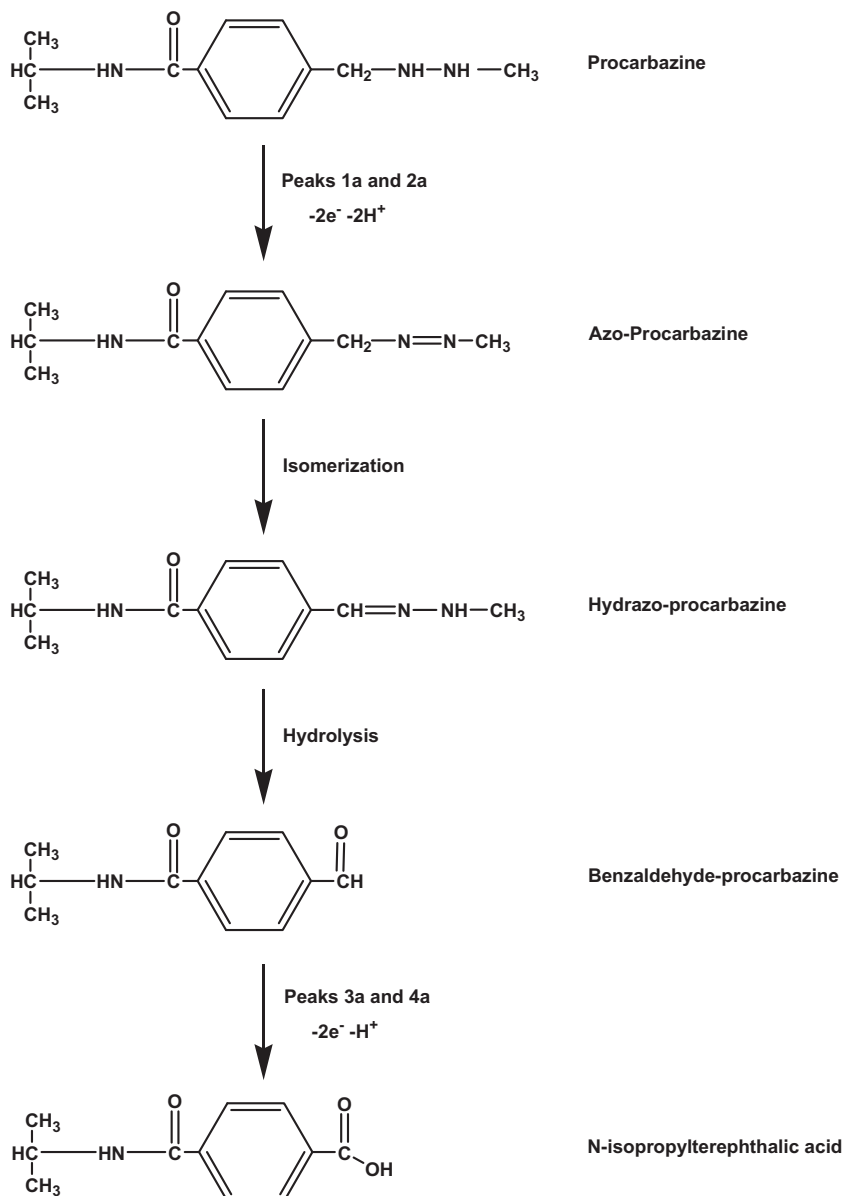
Electrochemical techniques are widely used in fundamental research to characterize the redox properties of drugs and biological compounds, mainly using polarographic and voltammetric techniques with different types of electrochemical substrates such as mercury and carbon electrodes, since the electrochemical data are correlated with the chemical structure and the pharmacological/biological activity of the species investigated, providing insights to help understanding biochemical mechanisms in living cells [7–18]. Recently numerous redox mechanisms of various antineoplastic drugs have been postulated from voltammetric studies [15–18].

To the best of our knowledge, the only electrochemical investigation of PCZ presented in the literature is a polarographic study of the influence of titanium (IV) ions, which are present on white cells of Hodgkin's and of leukemia patients, in the oxidation of PCZ by air, under physiological pH [19]. That study reveals that PCZ presents four reduction waves with half-wave potentials at  $-0.61$ ,  $-0.93$ ,  $-1.04$  and  $-1.30$  V and that titanium (IV) coordinates PCZ, causing a significant inhibition on its air oxidation, especially for oxidation catalyzed by copper (II) ions [19].

This work presents, for the first time, a study of the electrochemical oxidation mechanism of PCZ hydrate, for a wide range of solution conditions, using cyclic, differential pulse and square-wave voltammetry, at glassy carbon electrode.

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**Scheme 1.** Oxidation mechanism of PCZ.

## 2. Experimental

### 2.1. Materials and reagents

Procarbazine hydrochloride (PCZ) was obtained from Sigma and used without further purification. A stock solution of 300  $\mu\text{M}$  PCZ was prepared in deaerated deionized water and stored in the dark at 4  $^{\circ}\text{C}$ .

Supporting electrolyte solutions of different pH/composition (2.0/HCl + KCl, 3.3/HOAc + NaOAc, 4.5/HOAc + NaOAc, 5.2/HOAc + NaOAc, 5.9/ $\text{NaH}_2\text{PO}_4$  +  $\text{Na}_2\text{HPO}_4$ , 7.2/ $\text{NaH}_2\text{PO}_4$  +  $\text{Na}_2\text{HPO}_4$ , 8.0/ $\text{NaH}_2\text{PO}_4$  +  $\text{Na}_2\text{HPO}_4$ , 9.2/ $\text{NaOH}$  +  $\text{Na}_2\text{B}_2\text{O}_7$ , 11.2/ $\text{NaOH}$  +  $\text{Na}_2\text{HPO}_4$ ) were prepared using analytical grade reagents and purified water from a Millipore Milli-Q system (conductivity  $\leq 0.1 \mu\text{S cm}^{-1}$ ) with ionic strength  $I = 0.1 \text{ M}$  according to the literature [20]. Microvolumes were measured using EP-10 and EP-100 Plus Motorized Microliter Pipettes (Rainin Instrument Co. Inc., Woburn, USA). The pH measurements were carried out on a Metrohm Herisau (Switzerland) pH-meter using a Scott Gerate glass combination electrode.

All experiments were done at room temperature,  $T = 298 \text{ K}$  (25  $^{\circ}\text{C}$ ).

### 2.2. Voltammetric parameters and electrochemical cell

Voltammetric experiments were carried out using a  $\mu\text{Autolab}$  potentiostat, running with GPES 4.9 software, Metrohm/Autolab, Utrecht, The Netherlands. Measurements were carried out using a GCE ( $d = 3.0 \text{ mm}$ ), a Pt wire counter electrode, and an Ag/AgCl (3 M KCl) as reference electrode, in a 2 mL one-compartment conventional electrochemical cell. The experimental conditions for differential pulse (DP) voltammetry were: pulse amplitude  $\Delta E = 50 \text{ mV}$ , pulse width  $\Delta t = 70 \text{ ms}$ , and scan rate  $\nu = 5 \text{ mV/s}$ . For square wave (SW) voltammetry the experimental conditions were: frequency  $f = 25 \text{ Hz}$  and potential increment  $E = 2 \text{ mV}$ , corresponding to an effective scan rate  $\nu_{\text{effective}} = 50 \text{ mV/s}$ . The GCE was polished using diamond spray (particle size 1  $\mu\text{m}$ , 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 supporting electrolyte and

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