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VOLTAMMETRIC OXIDATION OF TRAZODONE*

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Abstract—The electrochemical behaviour of trazodone (TRZ), 2-{3-[4-(*m*-chlorophenyl)-1-piperazinyl] propyl}-1,2,4-triazolo-[4,3 *a*]pyridin-3(2H)-one hydrochloride has been investigated in aqueous media as a function of pH by cyclic voltammetry, coulometry and exhaustive electrolysis at solid electrodes.

The evolution of the *uv*-spectrum during electrolysis and TLC of the organic extracts have been realized. Interpretation of the results and a comparative study of a trazodone metabolite 1-*m*-chlorophenylpiperazine dihydrochloride (mCPP) have permitted the elucidation of the redox behaviour of trazodone, to point out different oxidation sites and distinct electrochemical processes depending on the pH of the solution.

Quantitative measurements of trazodone within the range 1×10^{-4} M–1×10^{-6} M have been realized at the carbon paste electrode (*cpe*) using the differential pulse technique.

INTRODUCTION

Trazodone (TRZ), 2-{3-[4-(*m*-chlorophenyl)-1-piperazinyl]propyl}-1,2,4-triazolo-[4,3*a*]pyridin-3 (2H)-one hydrochloride, is a triazolopyridine derivative with antidepressant activity, that is chemically unrelated to current antidepressants and has been recently introduced in clinical practice[1, 2]. As reported in the literature[3–6], this molecule[3–6] is extensively metabolized *in vivo*, mainly through oxidative processes giving rise to piperazine N-oxide structures and hydroxy functions on both pyridine and benzene nucleus (Fig. 1). The mechanism of action of trazodone is not yet fully understood and is still under extensive investigations[1, 2].

The present paper will be devoted to the study of the redox behaviour of trazodone at solid electrodes in aqueous media. The electrochemical behaviour of trazodone has not yet been reported, except in a recent work of Suckow dealing with the analytical determination of trazodone and its metabolites using HPLC with electrochemical detection[7].

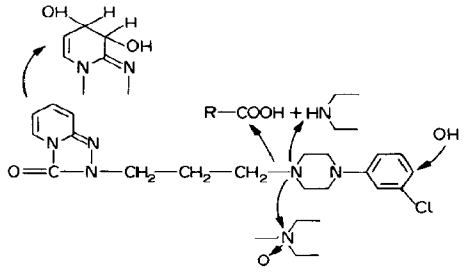

Fig. 1. Trazodone and several literature reported *in vivo* metabolites[3–6].

EXPERIMENTAL

Instrumentation

Linear scan and differential pulse voltammetric measurements have been carried out using a Bruker E 100 polarograph associated to a Hewlett–Packard type 7004 B recorder. Cyclic voltammetry has been realized with the PAR 174 A and 175 units associated to a PAR recorder type RE 0074. A three electrode system was used: the reference electrode was a saturated calomel electrode (*sce*) a platinum wire serving as auxiliary electrode. Two working electrodes based on carbon substrate were used: a carbon paste electrode (*cpe*) (Metrohm EA 207) prepared from standard paste (Metrohm EA 207 C; area: 50.3 mm^2), and a glassy carbon electrode (*gce*) (Metrohm AG; area: 19.6 mm^2).

Controlled potential coulometric measurements and large scale electrolysis have been performed with a PAR potentiostat Model 173 and a PAR digital coulometer Model 179 in a three electrode cell 9660 containing a cylindrical platinum gauze as working electrode (diameter: 3.6 cm, height: 2 cm). *uv*-absorption spectra of trazodone solutions and electrolyzed solutions were recorded with a Beckman DB/T and a Cary 219 *uv/vis* spectrophotometer. Thin-layer chromatography (TLC) of the organic

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extracts has been performed on Kieselgel 60 F 254 plates under conditions reported in current literature[4].

Reagents and solutions

Trazodone hydrochloride stock solutions were prepared by direct dissolution in bi-distilled water. Solutions under voltammetric investigations were prepared in 0.1 M phosphate buffers in the presence of methanol (20%), the apparent pH being adjusted with sulfuric acid or sodium hydroxide solutions. Coulometric and exhaustive electrolysis were carried out on aqueous solutions of TRZ. Dissolved oxygen was removed before measurements by passing purified nitrogen into the solutions during 10 min. All the assays were run at room temperature except quantitative measurements which have been performed in a thermostatic cell at 25.0 ± 0.1°C. Trazodone metabolite, 1-*m*-chlorophenylpiperazine dihydrochloride (mCPP) was obtained from Aldrich Chemie (Benelux). All reagents were of analytical grade and were used without any further purification.

RESULTS AND DISCUSSION

Cyclic voltammetry of trazodone

The reduction of the molecule is not observed at the two types of carbon electrodes used. However, the electro-oxidation of trazodone is well defined and occurs in two steps at high positive potentials very close to the solvent evolution (Fig. 2). Cyclic voltammetric measurements performed on 1×10^{-4}M trazodone solutions in the presence of 20% methanol show an irreversible nature of the peaks at both electrodes in the range of scan rates comprised of between 5 and 500 mV s^{-1} and in the entire pH range investigated. The anodic process is diffusion controlled as shown by the linear relationship existing between peaks current *I*p and the square root of scan rate. At the *gce*, cathodic peaks are not detected by reversing the scan direction after the first or the second anodic peak. However at the *cpe* by increasing the sensitivity of the measurement, we may detect on the reverse scan slight and closely spaced cathodic peaks (Fig. 2). If the scan is reversed after the second anodic peak, the cathodic peaks appear to a greater extent; moreover newly overlapping peaks may be detected. In the second anodic run, we observe the corresponding oxidation peaks. The presence of these quasi reversible couples located at less positive potentials than the parent compound suggests that a chemical reaction subsequent to the electron step occurs, giving rise to species more readily oxidized than trazodone. The number and the relatively low intensity of these redox couples compared to trazodone oxidation peaks suggest a complex nature of the oxidation process of trazodone.

The study of trazodone oxidation as a function of pH permits us to point out the appearance of these redox couples in acidic media, however their intensity diminishes progressively till pH 8.5 and the couples are no longer present at higher pH values. The intensity of the oxidation peaks and the potential of the second peak were found to be pH independent. However, by increasing the pH, the potential of the first peak is shifted to less positive values till pH 7.5, then becomes almost pH independent (Fig. 3). Basically, two linear regions are obtained, one between pH 1 and 7.5 with a slope around 50 mV/pH and one between pH 7.5 and 12 with a slope of 15 mV/pH. As the intersection of the curves is located around pH 7.5, close to the pKa of the piperazine moiety[8], the first trend corresponds to the conditions where the molecule is oxidized in its monoprotonated form.

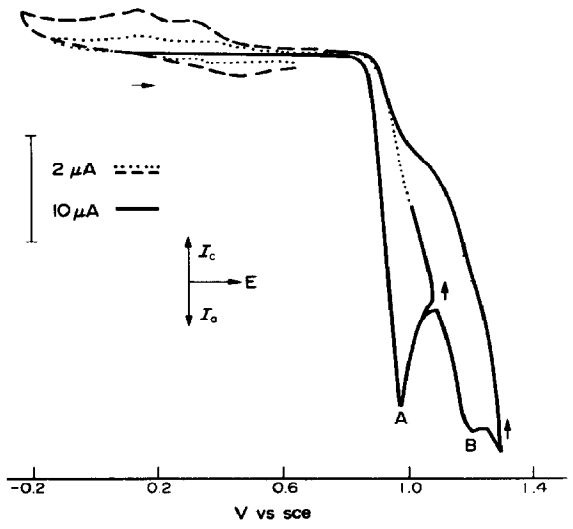

Fig. 2. Cyclic voltammetry of TRZ; 1×10^{-4}M; methanol 20%.

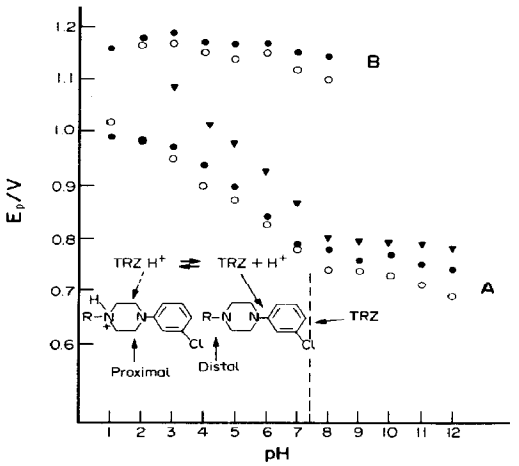

Fig. 3. Peak potential evolution as a function of pH. [TRZ] = 1×10^{-4} M; methanol 20%. • *cpe*, o *gce*, A: first peak; B: second peak, ▼ [mCPP] = 1×10^{-4} M; methanol 20%.

Coulometry and controlled potential electrolysis of trazodone

Controlled potential oxidations realized by holding the potential of the platinum working electrode at the first peak potential suggest the occurrence of a two electron oxidation process in acidic and basic media. The completeness of the reaction is followed by cyclic voltammetry at the *cpe* and by running the *uv* spectra as a function of time.

The evolution of the *uv* spectrum during the course of the electrolysis suggests that the first oxidation step occurs on the piperazine ring of the molecule (Fig. 4). Indeed, as soon as the electrolysis proceeds in neutral medium, we observe a decrease of the absorption peak at λ max 245 nm corresponding to the chlorophenyl-4-methylpiperazine moiety[8].

Thin-layer chromatography (TLC) of the organic extracts of the electrolyzed products gave several spots with *Rf* values closely related to the metabolites reported in the literature[4]. Attempts to realize oxidations at higher positive potentials were unsuccessful due to the restricted available anodic potentials at the platinum electrode.

Cyclic voltammetry of trazodone metabolite (mCPP)

The study of mCPP, by cyclic voltammetry at the *cpe* as a function of pH, offers further insight into the oxidative process of trazodone. The molecule is oxidized in one irreversible diffusion controlled step, giving a well defined peak whose intensity is pH independent and of the same magnitude as the trazodone first peak intensity. The peak is shifted to less positive potentials, with a slope of 60 mV/pH, by increasing the pH till 8, then becomes pH independent. As with trazodone, by running the cyclic voltammograms of mCPP, we may observe redox couples appearing at less positive potentials (Fig. 5). These couples are continuously present in acidic media and at pH values lower than 9 but are no more observed at higher pH values.

From the comparative study of trazodone and 1-*m*-chloropenylpiperazine, we are able to assume that the first oxidation step of trazodone is located on the piperazine ring. We may postulate that when the aliphatic nitrogen of the piperazine ring, distal to the benzene ring, is protonated ($TRZH^+$), oxidation occurs on the proximal nitrogen with possible formation of benzene hydroxylated forms reversibly and more readily oxidized than the parent compound (Fig. 3). This phenomenon might explain the low yield of the redox couples detected in cyclic voltammetry, their intensity being directly related to the ratio $TRZH^+/TRZ$, that is to the pH of the solution. Above pH 8.5, oxidation might exclusively occur at the most basic piperazine nitrogen (distal) following the well established aliphatic tertiary amine oxidation pathway[9–11].

Taking into account that the oxidation of mCPP closely resembles the oxidative process of the piperazine moiety of trazodone and by considering the structures of the *in vivo* metabolites of trazodone, we may assume that the second oxidation step of trazodone occurs at the triazolopyridine moiety of the molecule.

From a quantitative point of view, the *cpe* is well suited for the sensitive determination of trazodone. Studies as a function of concentration at various pH showed two anodic peaks in the range of concentration investigated, 1×10^{-4}M–1×10^{-6}M. Reproducibility has been tested running several scans on the same surface at pH 3 and using the differential pulse mode on a 1×10^{-6}M TRZ solution. The variation coefficient for seven measurements is 4% and the detection limit 1×10^{-7}M.

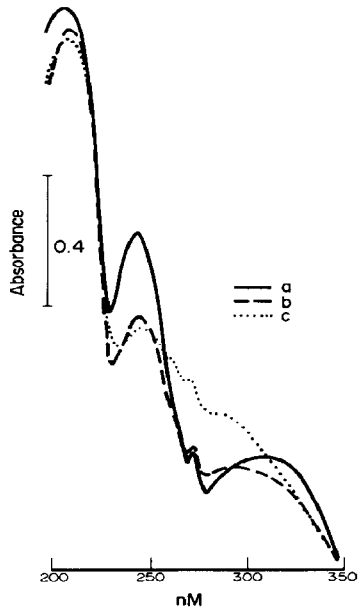

Fig. 4. [TRZ] = 2.5×10^{-5}M; KCl 0.01 M. *uv* spectrum evolution during controlled potential electrolysis (first peak). (a) After 0 F mol^{-1}. (b) After 1 F mol^{-1}. (c) After 2 F mol^{-1}.

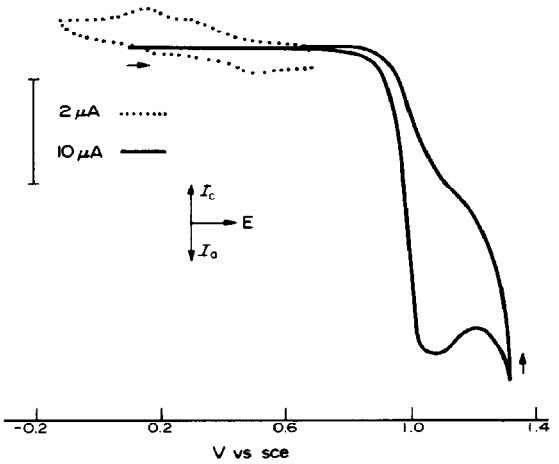

Fig. 5. Cyclic voltammetry of mCPP; 1×10^{-4} M; methanol 20%; pH = 3.0; scan rate: 20 mV s^{-1}; *cpe*.

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