SPECTROELECTROCHEMICAL AND THEORETICAL STUDY OF THE REDOX ACTIVATION OF ANTHRAQUINONE ANTITUMORAL DRUG MITOXANTRONE

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Mitoxantrone (Fig. 1) is an aminoanthraquinone, structurally related to doxorubicin – an anthracyclin antibiotic, used as an antitumoral drug due to its interaction with DNA (1, 2). However, besides their benefic action, these drugs possess also an undesirable toxicity. The generally accepted mechanism for this process implies the mono or bielectronic reduction of the drug with the appearance of intermediate species which may mediate the electron transfer to molecular oxygen, forming the superoxide anion radical and other reactive oxygen species, responsible for the cellular damage and cardiotoxicity (3 - 5). This process is usually called "reductive activation" of the drug.

The aim of the present study is to investigate the oxido-reduction behaviour of mitoxantrone (represented as AH_2, due to the presence of the dissociable phenolic groups) in protic (phosphate buffer) and aprotic media (dimethylsulfoxide, DMSO) by coupled electrochemical and spectral techniques, in order to identify the intermediate species and to examine the possibilty of electron transfer from the different intermediates to molecular oxygen.

The cyclic voltammetry at stationary and rotating platinum disc electrode (RDE) in the range 0 ÷ -1.7 V point out in aprotic media two succesive waves at –0.7 V and –1.52 V, corresponding, according to the usual electrochemical criteria, to the quasireversible monoelectronic reduction of the substrate to the anion radical ($AH_2^{-\cdot}$) and respectively, dianion (AH_2^{2-}). The prewave observed around –0.3 V disappears on succesive scans and, based on the linear variation of the peak current with the sweep rate, was assigned to an adsorption wave. If the scan is extended to positive potentials, the aspect of the cyclic voltammograms is different if the potential sweep is initiated with reduction or oxidation. If the scan is started by oxidation (Fig. 2), a bielectronic wave at +1.6 V is apparent and a new reduction wave is visible around –0.3 V, *i.e.* at more positive potentials as against the redox couple $AH_2/AH_2^{-\cdot}$. This new wave was assigned to a species resulting from the bielectronic oxidation of the drug, *i.e.* the tetraquinone (A).

In order to get a deeper insight into the redox mechanism of mitoxantrone, optical spectra were performed during the chemical (tetrabutylammonium hydroxide, TBAOH) and electrochemical oxido-reduction using *in-situ* techniques. Similitude of the results of the chemical and electrochemical reduction indicate an analogous action of the electrogenerated base and chemical base and allows the identification of the following intermediate species: $AH_2^{-\cdot}$ AH^-, $A^{2-\cdot}$. Electrochemical oxidation of the previous reaction mixture recovers the initial compound and leads finally to the tetraquinone (A). The general mechanism of the oxido-reduction of mitoxantrone consists of a sequence of electron and proton transfer reactions. Semiempirical AM1 MO calculations were performed in order to rationalise the experimental data and to evidence which are the electronic structural features implied in the redox reactivity, as well as to see if the reductive activation of molecular oxygen by the reduction intermediates is possible. Relevant electronic parameters used in the discussion of reactivity in redox process are: the absolute (vertical) and adiabatic ionization potentials and electronegativities. Analysis of the energetics of the different reduction and oxidation steps shows that the anthraquinone moiety is responsible for the redox properties of the drug and supports the proposed reaction mechanism. The reactivity towards molecular oxygen was examined for both ground ($^3\Sigma_g$) and singlet ($^1\Delta_g$) states of oxygen. The results point out smaller tendency to reductive activation of mitoxantrone as against doxorubicin and epirubicin, in agreement with its lower cardiotoxicity.

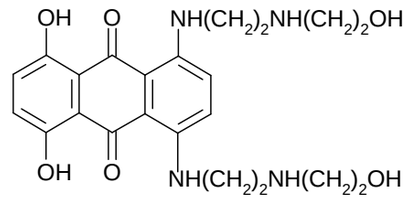

Fig. 1 Chemical formula of mitoxantrone.

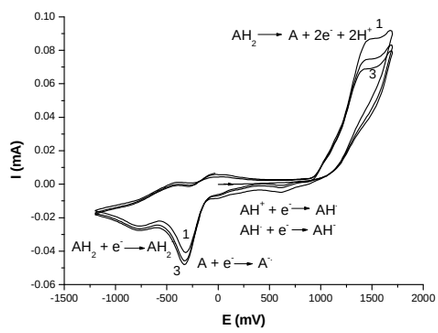

Fig. 2 Cyclic voltammograms of mitoxantrone (1.34×10^{-4}M) in DMSO, with initial oxidation sweep, deaerated media, sweep rate of 200 mV/s.

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