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Nonaqueous electrochemical oxidation of tamoxifen

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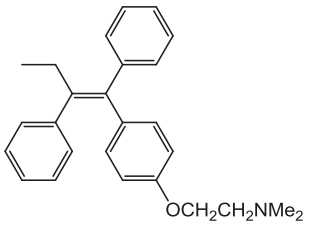
ABSTRACT

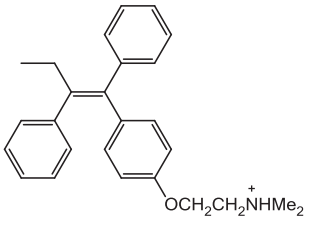
The electrochemical oxidation of the chemotherapeutic anti-cancer agent tamoxifen, **1**, was studied by voltammetry and electrolysis. Three successive one-electron anodic reactions were observed for **1** in dichloromethane containing weakly-coordinating $[B(C_6F_5)_4]^-$ as the supporting electrolyte anion. The first (totally irreversible) oxidation (*ca* 0.64 V *vs* ferrocene) occurs at the tertiary amine, giving a putative amine radical cation $\mathbf{1}^+\bullet$ that abstracts a hydrogen atom, most likely from solvent, to give the corresponding ammonium ion $\mathbf{1\text{-}H}^+$. The latter is responsible for the two further one-electron oxidations, which take place at the triarylethenyl part of the molecule ($E_{1/2}$ values of 0.94 V and 1.33 V *vs* ferrocene). Bulk oxidation of **1** at $E_{appl} = 0.6$ V produces the ammonium ion $\mathbf{1\text{-}H}^+$, which can be cathodically reduced back to neutral tamoxifen in an overall chemically reversible process. The present findings are not consistent with the mechanism described in previous literature for the anodic oxidation of tamoxifen.

1. Introduction

Tamoxifen, [Z-1-[4-(2-dimethylamino)ethoxy]phenyl-1.2-diphenylbut-1-ene], **1**, is a selective estrogen receptor modulator (an "antiestrogen") used in the treatment of human breast cancer [1,2]. It is widely accepted that the oxidative metabolism of tamoxifen by cytochrome P450 and other enzymes produces metabolites that may play a role in adverse side effects of the drug [3]. A better understanding of the biomedical outcomes of tamoxifen has been hampered, in part, by the scarcity of information about the redox mechanisms of tamoxifen and its metabolites [3]. Electrochemical methods have often proven worthwhile in modeling metabolic redox reactions [4–6]. However, although voltammetric methods have been described for the electrochemical analysis of tamoxifen down to trace levels [7–9], neither the effects of different electrolyte media on its electrochemical behavior, nor mechanistic aspects of its redox reactions have been well explored. The present paper, which appears to be the first report on the electrochemical oxidation of tamoxifen under nonaqueous conditions, is able to describe the oxidation mechanism of **1** under mild electrolyte conditions, and offer comments on previous assignments [7–9] of its oxidation products under protic conditions.



Tamoxifen (**1**)



1-H$^+$

2. Experimental

2.1. General

Electrochemical procedures were carried out under nitrogen in a Vacuum Atmospheres drybox. Dichloromethane was purified and dried by passing it through an alumina-based solvent system under argon. A previously published procedure [10] was employed for the preparation of $[NBu_4][B(C_6F_5)_4]$. Commercial sources were used to obtain tamoxifen (Combi-Blocks, San Diego, CA, used as received) and $[NBu_4][PF_6]$ (Tokyo Chemical Industry). The latter was recrystallized from absolute ethanol and vacuum dried at 373 K. Elemental analyses were performed at Robertson Laboratories.

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2.2. Electrochemistry

Three-electrode cells were employed for voltammetry and electrolysis experiments. For voltammetry experiments, a platinum wire counter-electrode was either immersed directly in the working compartment or separated from it by a fine frit. For electrolysis experiments, a platinum gauze electrode, separated from the working compartment by a fine glass frit, was employed as a counter-electrode. In both cases, the experimental reference electrode, immersed in an electrolyte solution separated by a fine frit from the working compartment, was a silver wire electroplated with silver chloride. All potentials reported in this paper are referenced to the ferrocene/ferrocenium potential [11], which was checked in each experiment *vs* the experimental Ag/AgCl potential by the ferrocene *in situ* method [12]. The working electrode for voltammetry was either a 2 mm gold or platinum electrode or a glassy carbon electrode (GCE) of 1–2 mm diameter, all of which were purchased from Bioanalytical Systems. Before each experiment, and if necessary after each scan, the electrode was buffed with diamond polishing compound, washed with nanopure water, and vacuum dried. The working electrode for bulk electrolysis was a platinum gauze basket that had been stored in nitric acid, washed with nanopure water, and either flame-dried or dried at 393 K for at least 24 h. The potentiostats employed were EG&G PARC 273 and 273A models, interfaced to a personal computer. Most CV scans were subtracted for background currents. Although analyte concentrations were usually about 1 mM, experiments on other concentrations over the range of 0.45 mM to 8.8 mM were included as will be noted in the text. Electrochemistry was carried out at either 298 K or ambient temperature.

3. Results

3.1. Voltammetry

The anodic electrochemistry of a number of multi-aryl ethylenes have been described [13–21]. Both triaryl ethylenes and tetraaryl ethylenes generally undergo two reversible one-electron oxidations, often at proximate $E_{1/2}$ potentials [14,16–18]. None of those systems, however, has a redox-active aryl substituent, as is so with the (dimethylamino)ethoxy group of tamoxifen. As shown below, arylethylene-based oxidations are also seen for tamoxifen, but they occur at potentials that are positive of the more facile oxidation of the dimethyamino group. We also note that the supporting electrolyte anion played an important role in giving reproducible voltammetric data. When the electrochemical medium was CH_2Cl_2/0.1 M $[NBu_4][PF_6]$, the cyclic voltammetry (CV) scans were irreproducible and gave irregular peak heights, as exemplified by Fig. 1. Improved voltammetric behavior was observed in CH_2Cl_2/0.05 M $[NBu_4][B(C_6F_5)_4]$, which was medium of choice for this study. As previously described [22–26], when compared to the anions traditionally used in nonaqueous solvents (*e.g.*, $[ClO_4]^-$, $[BF_4]^-$, $[PF_6]^-$), $[B(C_6F_5)_4]^-$ and other weakly-coordinating anions (WCAs) tend to form more soluble salts of positively-charged homogeneous electrolysis products, thereby minimizing electrode adsorption and "blockage" problems. Furthermore, WCAs are inherently less nucleophilic than are the traditional anions, a property that virtually eliminates the reaction of the electrolyte anion with radical cations.

A typical CV scan of tamoxifen in CH_2Cl_2/0.05 M $[NBu_4][B(C_6F_5)_4]$ is shown in Fig. 2. Of the three anodic waves, only the second was chemically reversible under all scan and concentration conditions. The first oxidation wave ($E_{pa}(1) = 0.64$ V at 0.2 V s^{-1}) has the shape of a totally irreversible one-electron process [27] (E_p-$E_{p/2} = 91$ mV, $\beta = 0.52$), which is characteristic of the oxidation of an aliphatic amine [28–30]. Furthermore, its potential fits well with those of simple tertiary amines (*e.g.* E_{pa} *ca* 0.64 V for NEt_3, 0.74 V for NMe_3 [29,31]). The second oxidation wave ($E_{1/2}(2) = 0.94$ V) has the characteristics of a one-electron reversible system (E_p-$E_{p/2} = 60$ mV, E_{pa}-$E_{pc} = 80$ mV, typical of what we measure for a quasi-Nernstian process under these conditions). Regarding the third wave, the fact that chemical reversibility was observed under some conditions [32] allowed us to assign a value of $E_{1/2}(3) =$ 1.33 V to this reaction.

Square-wave voltammetry (SWV) (see Fig. 3) confirmed that the second oxidation was the only quasi-Nernstian process among the three processes, based on the markedly greater current for the second wave [33].

As will be shown below, the follow-up product of the first (amine-based) oxidation of tamoxifen is the simple tertiary ammonium compound **1-H**$^+$, formed apparently when the putative radical cation **1**$^{+\bullet}$ abstracts hydrogen very quickly from an H-atom donor (most likely the solvent). Taken together, the voltammetry and electrolysis experiments are consistent with the reaction sequence of Eqs. (1)–(3) to

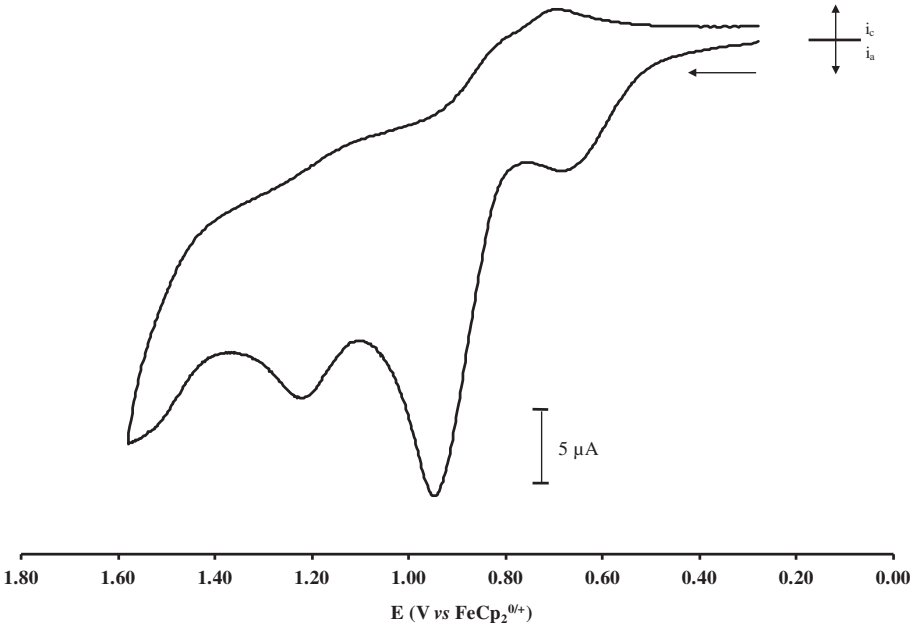

Fig. 1. CV scan of 1.0 mM **1** in CH_2Cl_2/0.1 M $[NBu_4][PF_6]$ at ambient temperature, 0.2 V s^{-1}, 2 mm GCE.