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Electrochemical Oxidation of Acetaminophen in the Presence of Barbituric Acid Derivatives

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Electrochemical oxidation of acetaminophen (**1**) in the presence of barbituric acid (**2a**), 1,3-dimethyl barbituric acid (**2b**), 2-thiobarbituric acid (**2c**) and 1,3-diethyl-2-thiobarbituric acid (**2d**) as nucleophiles in aqueous solution has been studied using cyclic voltammetry and controlled-potential coulometry. The results indicate that the *p*-quinone imine derived from electrooxidation of acetaminophen (**1**) participates in a Michael addition reaction with **2a-d** to form the corresponding barbituric acid derivatives (**7a-d**). In addition, the homogeneous rate constants were estimated by comparing the experimental cyclic voltammetric responses with the digital simulated results. The electrochemical synthesis of **7a-d** has been successfully performed in an undivided cell in good yields and purity at biological pH.

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Electrochemistry provides a versatile means for the selective reduction and oxidation of organic compounds. The importance of an electrochemical synthesis lies not only in the selectivity of the reaction, but also in the formation of electrons at the electrode surface.[1,2] Since the electrons are reagent free, pollution of the environment by spent reagents can be avoided. In addition, electrosynthesis can lead to efficient and sometimes unexpected synthesis of compounds, which cannot be easily prepared by conventional organic synthesis.[1,2] As an electroactive substance, acetaminophen (paracetamol) has also attracted much interest. Acetaminophen (paracetamol) (N-acetyl-*p*-aminophenol) is a popular, antipyretic and non-steroidal anti-inflammatory drug.[3] It is the preferred alternative to aspirin, particularly for patients who cannot tolerate aspirin[4] It has been shown that *N*-acetyl-*p*-benzoquinone-imine (*NAPQI*) is the main in vivo and in vitro oxidation product of acetaminophen.[5]

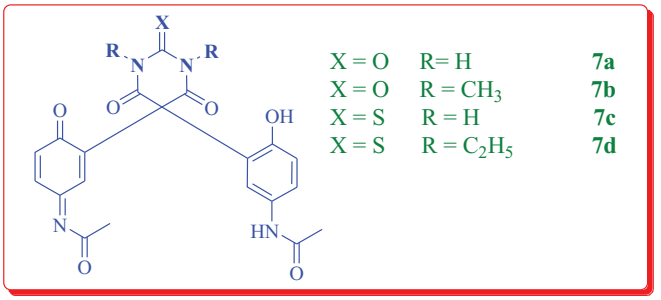
On the other hand barbituric acid and its derivatives are widely used in the preparation of barbiturates, dyes, and polymerization catalysts.[6] Also barbituric acid derivatives are well known to possess antibacterial,[7] sedatives,[8] herbicides,[9] fungicides[10] and antiviral agents.[11] Our previous studies show that the electrochemically generated *NAPQI* is a reactive intermediate and as a Michael acceptor, participates in different types of reactions[12–16] However, until now, no report has been published about the electrooxidation of acetaminophen in the presence of barbituric acid derivatives. In this work electrochemical oxidation of acetaminophen (**1**) has been studied in the presence of barbituric acid (**2a**) 1,3-dimethylbarbituric acid (**2b**), 2-thiobarbituric acid (**2c**) and 1,3-diethyl-2-thiobarbituric acid (**2d**) as nucleophiles (Fig. 1).

Some electrochemical techniques such as: cyclic voltammetry using diagnostic criteria derived by Nicholson and Shain for various electrode mechanisms and controlled-potential coulometry were used. These methods provide a powerful independent route for quantitative characterization of complex electrode processes.[17] The present work has led to the development of a facile electrochemical method for the synthesis of new and unique barbituric derivatives in good yield and purity.

Experimental

Apparatus and reagents.— Cyclic voltammetry and controlled-potential coulometry were performed using an Autolab model PG-STAT 20 potentiostat/golvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disk (1.8 mm diameter), and platinum wire was used as counter electrode. The working electrode used in controlled-potential coulometry was an assembly of four carbon rods (6 mm diameter and 4 cm length) and a large platinum gauze constitute the counter electrode. The working electrode potentials were measured versus SCE (all electrodes from AZAR electrode). The homogeneous rate constants were estimated by analyzing the cyclic voltammetric responses using the cyclic voltammetry digital simulation DIGIELCH software.[18] All chemicals (acetaminophen, barbituric acid, 1,3-dimethylbarbituric acid, 2-tiobarbituric acid and 1,3 diethyl 2-tiobarbituric acid) were reagent-grade materials from Aldrich and phosphate salts and other inorganic salts were of pro-analysis grade from E. Merck. These chemicals were used without further purification.

*Synthesis of compounds **7a-d**.*— A solution (ca. 80 mL) of phosphate buffer (0.2 M, pH = 7.2) containing 2 mmol of acetaminophen (**1**) and 2 mmol of 2-thiobarbituric acid (**2c**) was electrolyzed in an undivided cell equipped with a glassy carbon anode and a large stainless steel gauze as cathode, at 25°C at 0.50 V versus SCE. The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted several times during the electrolysis (due to the formation of a film of product at the surface of the electrode) and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of phosphoric acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and was washed several times with water. After recrystallization, products were characterized by IR, ^{1}H NMR and MS.



*Characterization of product **7a** ($C_{20}H_{18}N_4O_7$).*— Mp > 273°C (Dec.). ^{1}H NMR (300 MHz DMSO-d$_6$) δ (ppm): 1.99 (s, 6H, methyl), 6.82–7.46 (m, 6H, aromatic), 9.27–9.86 (broad, NH, OH), 11.48 (s, NH: barbituric acid). IR $_{(KBr)}$: 3219, 3061, 2926, 1616, 1712, 1502, 1408, 1234, 1233 cm^{-1}.

*Characterization of product **7b** ($C_{22}H_{22}N_4O_7$).*— M.p > 270°C (Dec.). ^{1}H NMR (300 MHz DMSO-d$_6$) δ (ppm): 2.01 (s, 6H methyl), 3.22 (s, 6H methyl), 6.88–7.46 (m, 6H, aromatic), 9.87–9.96 (broad, NH, OH). IR$_{(KBr)}$: 3361,3300, 3280, 1640, 1600, 1417, 1273,

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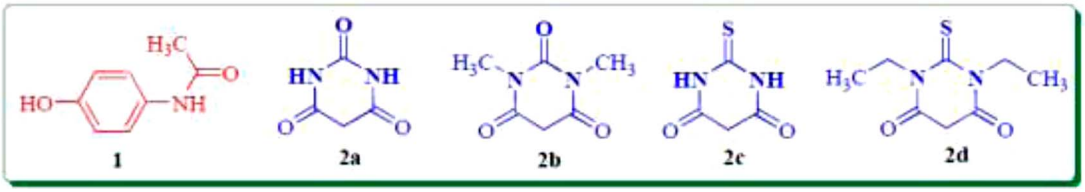


Figure 1. Chemical structure of acetaminophen (**1**), barbituric acid (**2a**), 1,3-dimethyl barbituric acid (**2b**), 2-thiobarbituric acid (**2c**) and 1,3-diethyl-2-thiobarbituric acid (**2d**).

1260,1257, 1240 cm^{-1}. MS; *m/z* (relative intensity) = 454(M^++2H., 2.5), 430 (36), 257 (13), 229 (88), 196 (33), 165 (34), 111 (66), 160 (95), 169 (100).

Characterization of product ***7c*** *($C_{20}H_{18}N_4O_6S$).*— M.p > 243°C (Dec.). ^{1}H NMR (300 MHz DMSO-d_6) δ (ppm): 1.98 (s, 6H methyl), 6.81–7.42 (m, 6H aromatic), 9.75 (s, 2OH), 9.83 (s, 2NH), 11.0 (broad, NH). $IR_{(KBr)}$: 3412, 2954, 2910, 2900, 1658, 1612, 1503,1463, 1376,1203 cm^{-1}. MS; *m/z* (relative intensity) = 442 (M^++2H., 3.5), 256 (2), 111 (6), 71 (14), 57 (26), 43 (34), 19 (100).

Characterization of product ***7d*** *($C_{22}H_{22}N_4O_6S$).*— M.p > 250°C (Dec.). ^{1}H NMR (300 MHz DMSO-d_6) δ (ppm): 1.13 (s, 6 H methyl), 1.96 (s, 6H, methyl), 4.36 (s, 4H, ethyl protons) 6.80–7.41 (m, 6H aromatic), 9.74 (s, 2OH), 9.82 (s, 2NH). $IR_{(KBr)}$: 3269, 2978, 2870, 1662, 1595, 1504, 1371,1342, 1261 cm^{-1}.

Results and Discussion

Voltammetric study.— Figure 2 curve a, shows cyclic voltammogram recorded for 1 mM acetaminophen (**1**) in aqueous solution containing 0.2 M phosphate buffer (pH 7.2). The voltammogram shows an anodic peak (A_1) in the positive-going scan and a cathodic counterpart peak (C_1) in the negative-going scan which corresponds to the transformation of acetaminophen (**1**) to N-acetyl-*p*-benzoquinone-imine (NAPQI) (**1a**) and *vice-versa* within a quasi-reversible two-electron process.[15,16] In these conditions, peak current ratio (I_p^{C1}/I_p^{A1}) nearly unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *p*-quinone imine produced (**1a**) at the surface of electrode under the experimental conditions.

The oxidation of acetaminophen (**1**) in the presence of 2-thiobarbituric acid (**2c**) as a nucleophile was studied in some details. Figure 2 (curve b) shows the cyclic voltammogram obtained for a 1 mM solution of **1** in the presence of 3 mM 2-thiobarbituric acid in aqueous solution containing 0.2 M phosphate buffer (pH 7.2). In these conditions, the cathodic counterpart of the anodic peak A_1 decreases. Furthermore, it is seen that proportional to the augmentation of potential sweep rate, the height of C_1 peak of **1** increases (Figure 3, curves a-e). A similar situation is observed when the 2-thiobarbituric acid to acetaminophen (**1**) concentration ratio is decreased. A plot of the peak current ratio (I_p^{A1}/I_p^{C1}) versus *v* for a mixture of acetaminophen (**1**) and 2-thiobarbituric acid (**2c**) confirms the reactivity of **1a** toward 2-thiobarbituric acid, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Fig. 3, inset). On the other hand the current function for A_1 peak, ($I_p^{A1}/v^{1/2}$), changes only slightly with increasing the scan rate.[17]

Controlled potential coulometry was performed in aqueous solution (0.2 M phosphate buffer, pH 7.2) containing 0.2 mmol of **1** and 0.2mmol of 2-tiobarbituric acid (**2c**) at 0.45 V *versus* SCE. The monitoring of electrolysis progress was carried out by cyclic voltammetry (Fig. 4). It is shown that anodic peak A_1 decreases proportionally to the advancement of coulometry. All anodic and cathodic peaks disappear when the charge consumption becomes about $3e^-$ per molecule of **1**. These observations allow us to propose the pathway in Scheme 1 for the electrooxidation of **1** in the presence of 2-tiobarbituric acid (**2c**).[19–21]

According to our results, it seems that the 1,4 (Michael) addition reaction of enolate anion **3c** to N-acetyl-*p*-benzoquinone-imine *(NAPQI)* (**1a**) is faster than other secondary reactions, leading presumably to the intermediate (**5c**). The oxidation of this compound

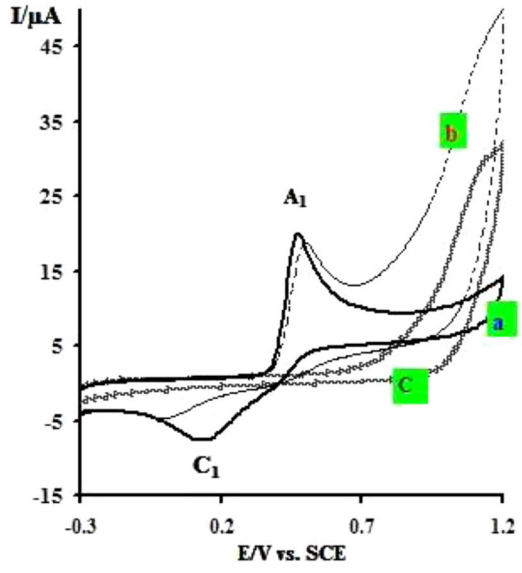


Figure 2. (a) Cyclic voltammogram of 1 mM acetaminophen (**1**) (b) Cyclic voltammogram of 1 mM acetaminophen in present of 3 mM 2-tiobarbituric acid (**2c**), (c) Cyclic voltammogram of 1mM 2-tiobarbituric acid in phosphate buffer solution (c = 0.2 M, pH = 7.2). Scan rate: 50 mV s^{-1}. $T = 25 \pm 1$°C.

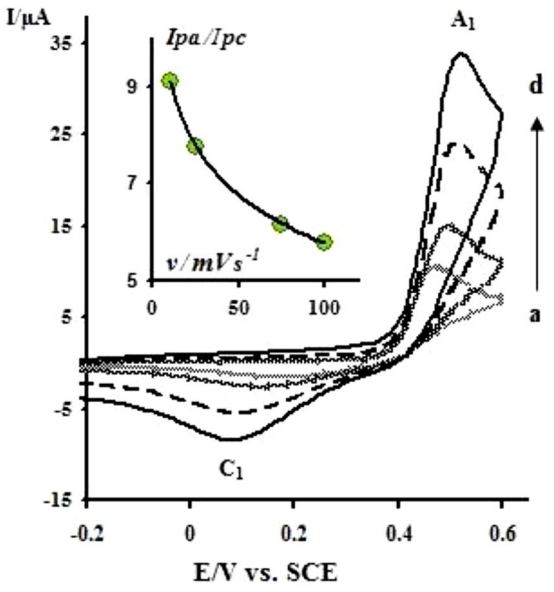


Figure 3. Typical voltammograms of 1 mM acetaminophen in the presence of 3 mM 2-tiobarbituric acid in phosphate buffer solution (c = 0.2 M, pH = 7.2) in various scan rates. Scan rate are: 10, 25, 75 and 100 mVs^{-1}.

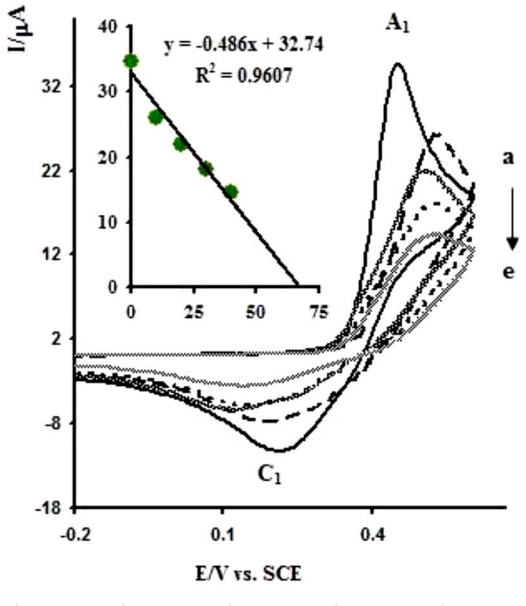


Figure 4. Cyclic voltammograms of 0.2 mmol acetaminophen in the presence of 0.2mmol 2-tiobarbituric acid in 0.2 M phosphate buffer, pH = 7.2 during controlled potential coulometry at 0.30 V vs. SCE, after consumption of: (a) 0.0, (b) 10, (c) 20, (d) 30 and (e) 40 C. Scan rate: 100 mVs^{-1}. Inset: variation of peak current vs charge consumed. $T = 25 \pm 1°C$.

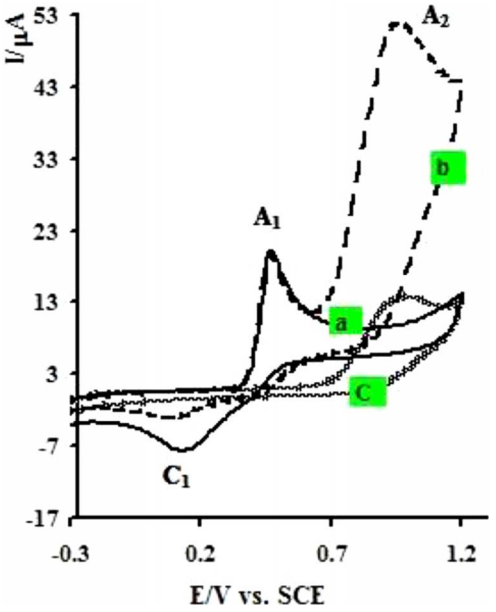
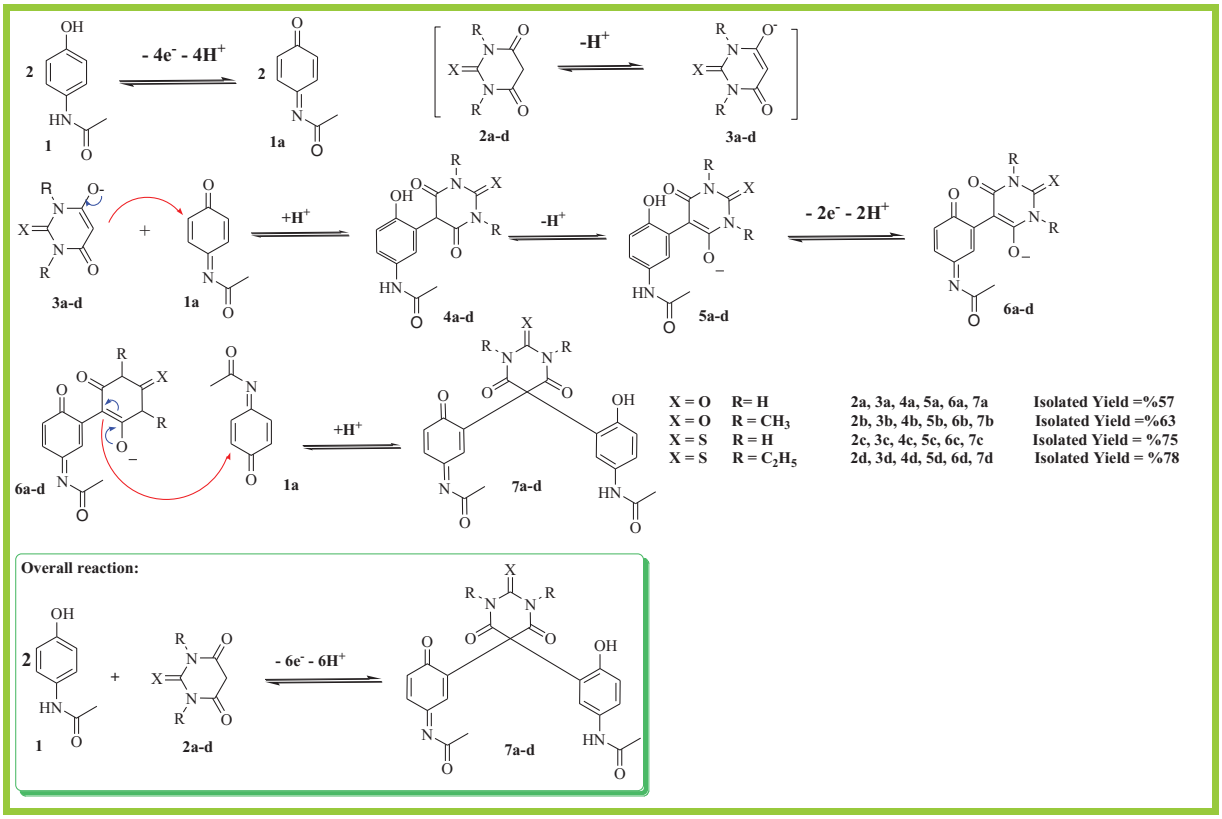


Figure 5. (a): Cyclic voltammograms of 1 mM acetaminophen (b) Cyclic voltammogram of 1 mM acetaminophen in the present of 3 mM 1,3- dimethylbarbituric acid (**2b**), (c) Cyclic voltammogram of 1mM 1,3-dimethylbarbituric acid in phosphate buffer solution (c = 0.2 M, pH = 7.2). Scan rate: 50 mV s^{-1}. $T = 25 \pm 1°C$.

(**5c**) is easier than the oxidation of parent starting molecule (**1**) by virtue of the presence of an electron-donating group. It can be seen from the mechanism written above that, as the chemical reaction [eqn. (2)] occurs, **1** is regenerated through homogeneous oxidation and hence, can be reoxidized at the electrode surface. Thus, as the chemical reaction takes place, the apparent number of electrons transferred increases from the limits of $n = 2$ to 3 electrons per molecule. The reaction product (**7c**) can also be oxidized at a lower potential than



Scheme 1. Proposed ECEC mechanism for the electrochemical oxidation of acetaminophen (**1**) in the presence of **2a-c**.

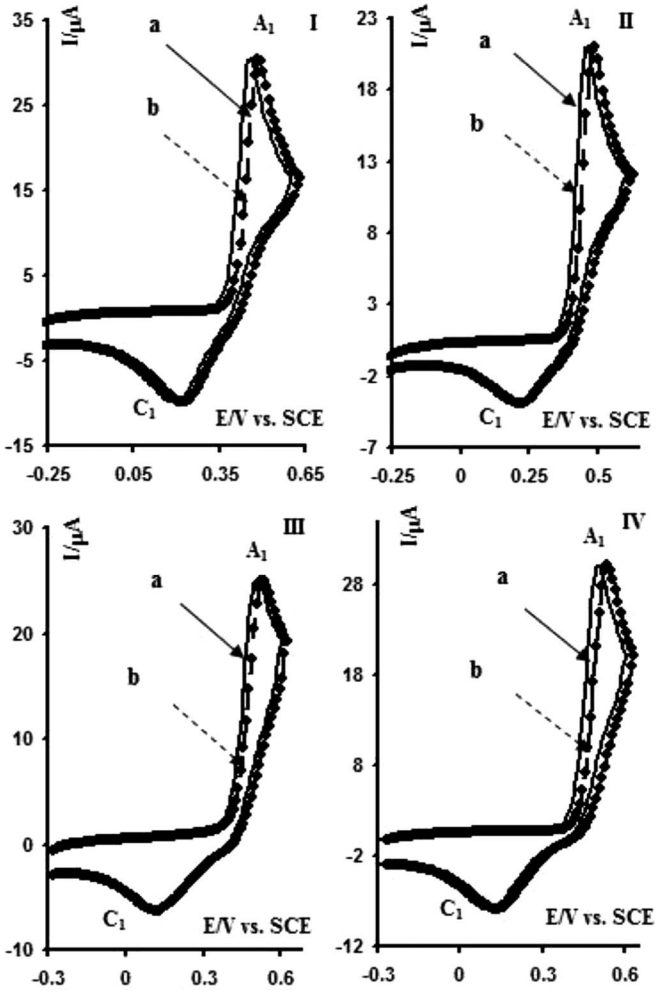


Figure 6. Cyclic voltammogrms of 1 mM acetaminophen (**1**) in the presence of (**I**) 3 mM barbituric acid (**2a**), (**II**) 1,3-dimethyl barbituric acid (**2b**), (**III**) 2-thiobarbituric acid (**2c**) and (**IV**) 1,3-diethyl-2-thiobarbituric acid (**2d**) at pH = 7.2, (a) experimental (b) simulated. Scan rate 100 mVs^{-1}.

the starting **1** compound. However, overoxidation of **7c** was circumvented during the preparative reaction because of the insolubility of the product in this medium. The mechanism was established by using IR, ^{1}H NMR, and MS techniques. In the mass spectrum of compound **7c**, molecular ion [M + 2H] was recorded. This mass is related to protonation of the NH groups[22–24] and is another proof for production of **7c** in electrooxidation of **1** in the presence of **2c**. The sum total voltammetry, coulometry and spectroscopy results imply on an *ECEC* electrochemical mechanism.[17] The proposed *ECEC* electrochemical mechanism is presented in Scheme 1.

The same results was obtained in electrooxidation of acetaminophen (**1**) in the presence of barbituric acid (**2a**), 1,3- dimethyl-barbituric acid (**2b**) and 1,3- diethyl 2-tio-barbituric acid (**2d**) (Fig. 5).

Digital simulation.— Based on proposed mechanism, the observed homogeneous rate constants of electrochemical oxidation of acetaminophen (**1**) in the presence of barbituric acid derivatives (**2a-d**) as nucleophile have been estimated by comparing the simulation results with those of the experimental cyclic voltammograms. The simulation was carried out assuming semi-infinite one-dimensional diffusion and planar electrode geometry. The experimental parameters such as analytical concentrations, E_{start} and E_{final} were entered for digital simulation according to the experimental conditions. The transfer coefficients (α) were assumed to be 0.5 and the formal potentials were obtained experimentally as the midpoint potential between the anodic and cathodic peaks (E_{mid}). The heterogeneous rate constants (0.002 cm s^{-1}) for the oxidation of acetaminophen (**1**) were estimated using experimental working curves.[25,26] All these parameters were kept constant throughout the digital simulation process. The parameter k_{obs} were allowed to change. There was good agreement between the simulated voltammograms with those obtained experimentally (Fig. 6). The calculated values of the second-order rate constants for the reaction of acetaminophen (**1**) with barbituric acid derivatives (**2a-d**) are shown in Table I.

Table I. Observed homogeneous rate costants, k_{obs} (M^{-1} s^{-1}), for the studied acetaminophen in the presence of barbituric acid (2a), 1,3-dimethyl barbituric acid (2b), 2-thiobarbituric acid (2c) and 1,3-diethyl-2-thiobarbituric acid (2d).

k^a_{obs} of **1a** with **3a**	k^a_{obs} of **1a** with **3b**	k^a_{obs} of **1a** with **3c**	k^a_{obs} of **1a** with **3d**
0.12 ± 0.01	0.19 ± 0.01	0.15 ± 0.01	0.21 ± 0.01

[a]Each second-order rate constant is the average of three determinations and is reported together with the standard deviation.

As can be seen, the correlation is quite satisfactory. The observed homogeneous rate constants (k_{obs}) of electrooxidation of acetaminophen with barbituric acid derivatives (**2a-d**) is closely related to the electron-donating strength of the substituted groups (X, R_1) on **2a-d**. The calculated observed homogeneous rate constants (k_{obs}) were found to vary in the order of k_{obs}(**3d**) > k_{obs}(**3b**) > k_{obs}(**3c**) > k_{obs}(**3a**). As can be expected the presence of electron-donating groups such as ethyl (**3d**) or methyl (**3b**) on nucleophile ring causes an increase in k_{obs}. Also according to the magnitude of k_{obs}, **3c** is much better nucleophile as compared with **3a** because of the presence of S atom in **3c**, instead of O atom in the structure of **3a**.

Conclusions

The present results complete the previous reports on the anodic oxidation of acetaminophen in aqueous solutions.[14] The results of this work show that acetaminophen is oxidized in water to its *p*-quinone imine (**1a**). The *p*-quinone imine generated is then attacked by the enolate anion of **3a-d** to form barbituric acid derivatives. The overall reaction mechanism for anodic oxidation of acetaminophen in the presence of barbituric acid and some of its derivatives as the nucleophile is presented in Scheme 1. The Michael addition reaction of these nucleophiles to the *p*-quinon imine (**1a**) formed leads to the formation of new and unique barbituric derivativesas final products, in good yield and purity.

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