Electrochemical sensing of phenacetin on electrochemically reduced graphene oxide modified glassy carbon electrode

MENG Xiao-tong[1], ZHU De-jing[1], JIANG Yu-hang[1], CAO Yue[1], SI Wei-meng[1,*], CAO Jun[1], LI Qiu-hong[1], LI Jiao[1], LEI Wu[2]

（1. *School of Materials Science and Engineering*, *Shandong University of Technology*, *Zibo* 255049, *China*;
2. *School of Chemical Engineering*, *Nanjing University of Science and Technology*, *Nanjing* 210094, *China*）

Abstract: It is known that the electrochemical determination of phenacetin, a widely used analgesic, is challenging because of the interference of the electroactive intermediate, acetaminophen. Phenacetin was proven to be electroactive in 1980s, but its electrochemical determination has not been widely reported. This determination on an electrochemically reduced graphene oxide (ERGO) electrode was investigated and compared with several nitrogen-doped graphene samples. Results indicate that ERGO has a higher current response and lower oxidation potential than nitrogen-doped graphene. An ERGO electrode as a phenacetin sensor has a detection limit of 0.91 μmol L^{-1}. The redox mechanism of phenacetin is inferred by electrochemical experiments, and the reactions under different pH values are proposed. Acetaminophen is considered to be the main intermediate and that does not interfere with the determination of phenacetin. But phenacetin obviously interferes with the response of acetaminophen, suggesting that the simultaneous detection of phenacetin and acetaminophen is not possible. Species such as Cu^{2+}, Al^{3+}, methanol, ethylene glycol, glucose, and ascorbic acid do not interfere with the determination of phenacetin.

Key words: Phenacetin; Acetaminophen; Electrochemical reduced graphene oxide; Electrochemical determination

1 Introduction

It is well-known that phenacetin was once a widely used analgesic. However, as a result of its carcinogenic properties and potential inducement of kidney-damage, it has been gradually withdrawn from the global market. Despite this, it is still a common adulterant in analgesic, compound pharmaceuticals, such as compound aspirin tablets. Therefore, it is of great importance to be able to sensitively and selectively analyze products for the presence of phenacetin. The electrochemical reactions of phenacetin were studied by Kissinger and colleagues in 1980s[1]. As has been previously reported, in the common voltammetry test, phenacetin can be transformed into acetaminophen[2,3]. Consequently, the determination of phenacetin is challenging, because the interference of these electroactive intermediates. To the best of our knowledge, the determination of phenacetin has not been widely reported, and the determination of acetaminophen is more concerned. On some well-constructed acetaminophen sensor, phenacetin did not generate an oxidation current at the working potential. Phenacetin was thus studied as an interferent in acetaminophen sensing[4]. Apart from that, graphene/ZnO composite has been used in the electrochemical sensing of acetaminophen and phenacetin simultaneously, but the detection limit of phenacetin was not given[5]. CdSe was also employed in the simultaneous determination of phenacetin and acetaminophen[6]. Nevertheless, the interfering between phenacetin and acetaminophen was not well-discussed in these reports.

Various graphene materials are widely used in acetaminophen sensors, including graphene aerogel[7], graphene oxide[8], reduced graphene oxide[9], graphene doped with heteroatoms[10]. Electrochemical reduced graphene oxide (ERGO) can be easily prepared on conducting electrode substrates for electrocatalytic applications and used intensively in electrochemical sensors. Also, nitrogen-doped graphene (NGE) has recently become one of the mostly studied doped graphene[11–14], where the doped nitrogen atoms (pyrrole-N, pyridine-N, graphitic-N, and pyridine-N oxide) play a key role in the enhanced reaction per-

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Corresponding author: SI Wei-meng, Associate professor. E-mail: siweimeng@foxmail.com

Author introduction: MENG Xiao-tong, Master student. E-mail: 251033197@qq.com

formance[15]. A variety of methods have been used to synthesize NGE containing various nitrogen species[11,15–19]. Unlike the study of acetaminophen sensors, the comparative study of these graphene as phenacetin sensing materials has not been reported.

In this reported work, the electrochemical behavior of phenacetin on various graphene materials was studied. NGE is considered to be unsuitable for the phenacetin determination, and electrochemical reduced graphene oxide (ERGO) was found to exhibit a higher response and lower overpotential for the electrooxidation of phenacetin. Also, the ERGO was used in the determination of phenacetin and a detection limit of 0.91 μmol L^{-1} was established. These experimental results showed that phenacetin interferes with the electrochemical determination of acetaminophen. Consequently, it is not possible to simultaneously determinate the concentration of acetaminophen and phenacetin on graphene. However, it was found that acetaminophen did not interfere with the electrochemical response of phenacetin, indicating that the ERGO was a good sensing material for phenacetin determination.

2 Experimental

2.1 Reagents and apparatus

GO was synthesized as reported before[20–22]. All chemicals were of analytical grade and used as received. Citric acid-phosphate buffer (CPS) was prepared with 0.2 mol L^{-1} Na_2HPO_4 and 0.1 mol L^{-1} citric acid. Phosphate buffer saline (PBS) was prepared by mixing 0.2 mol L^{-1} NaH_2PO_4 and 0.2 mol L^{-1} Na_2HPO_4.

Scanning electron microscopy (SEM) was carried out on an FEI SIRION microscope. The CHI660E electrochemical system (CH Instrument, Shanghai, China) was used for all the electrochemical measurement. The conventional three-electrode system was employed using a bare or modified glassy carbon electrode (GCE) as a working electrode, a saturated calomel electrode (SCE) as a reference electrode and a platinum wire as a counter electrode, where the diameter of GCE is 3 mm and the stem is PTFE.

2.2 Preparation of ERGO/GCE and NGE/GCE

ERGO was prepared via a usual two-step method where a graphene oxide (GO) modified glassy carbon electrode was modified with a GO solution (1 mg mL^{-1}) using a drop-casting method. After air drying, the GO was reduced in a phosphate buffer solution using cyclic voltammetry (CV) over a potential range of −1.7-0 V for 10 cycles. It was found that the resulting ERGO possessed a higher roughness surface, compared with chemically-reduced GO[23]. Various NGEs were also prepared using the traditional hydrothermal method using GO as the raw material. In a typical process, a reducing/doping agent was added to the GO dispersion (1 mg mL^{-1}). The mixture was sonicated for 2 h and then sealed in a Teflon-lined autoclave and maintained at 130 °C for 8 h. Subsequently, this suspension was washed repeatedly to remove any unreacted reducing/doping agent. An NGE containing pyridine-N oxide (NGE-N) was prepared using vitamin B3 as the reducing/doping agent as previously reported[18]. NGE with abundant graphitic-N (NGE-A) was prepared using 2-aminopyridine as the reducing/doping agent[11]. NGE with pyridine-N and pyrrole-N (NGE-U) was prepared using urea as the reducing/doping agent. The NGE-A, NGE-N, NGE-U were individually dispersed in DMF (0.5 mg mL^{-1}) and each was individually drop-cast onto a separate polished GCE.

3 Results and discussion

As shown in Fig. 1a and 1b, both GO and ERGO have very rough surfaces. After the electrochemical reduction, this roughness is further enhanced (Fig. 1d), as compared with GO (Fig. 1c). This unique morphology increases the amplification of the phenacetin signal. Also, when compared to other NGEs (Fig. 1f-g), the ERGO (Fig. 1e) possesses higher surface area, which favors an increase in the number of active sites for electrochemical reaction, and therefore enhances the signal response.

The relative electrocatalytic activity of the ERGO and various NGEs for phenacetine was ex-

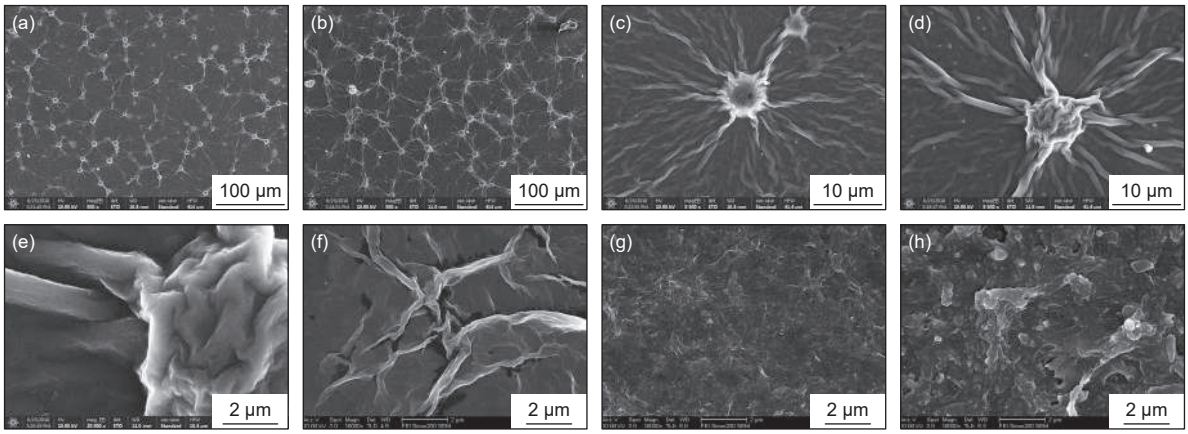


Fig. 1 SEM images of (a,c) GO , (b,d,e) RGO, (f) NGE-A, (g) NGE-N and (h) NGE-U.

amined using CV in PBS containing 0.05 mmol L^{-1} phenacetin (pH=4.9, scan rate: 100 mV s^{-1}). Fig. 2a and 2b, show the 1st and 2nd cycles of each experiment.

As shown in Fig. 2a, a significant oxidation peak is present in the CV of each electrode (Peak I), which is resulted from the oxidation of phenacetin. This reaction involves the formation of a quinone-imine cation intermediate, which is quickly hydrolyzed to produce N-acetyl-*p*-benzoquinone imine (NAPQI)[3]. NAPQI is then reduced to acetaminophen, which corresponds to the oxidation current seen in peak II in Fig. 2a. The quasi-reversible redox peak at ~0.45 V of 2nd cycle corresponds to the redox of acetaminophen (Fig. 2b). Furthermore, as shown in Fig. 2a and 2b, the ERGO modified electrode (curve a) exhibits a higher peak current and lower overpotential for this reaction. This is surprising in light of the fact that NGE has proven to have good catalytic activity for acetaminophen[11]. ERGO exhibits a higher response to acetaminophen than all of the other NGE electrodes. As revealed before, GO tends to self-assembly into highly dense but porous carbon in slow evaporation[24]. The shrinkage of the 3D network can be derived in the capillary compression, which is in favor of the enhanced response. Also, as previously reported, chemically prepared nitrogen-doped graphene samples usually have low surface roughness[11,18], which may hinder the kinetics of the electrochemical reactions at their surface, which would produce a muted signal response.

To further investigate the mechanism of the electrode reactions, the effect of pH value on the electrochemical behavior was evaluated by CV testing in buffered solutions containing 0.1 mmol L^{-1} phenacetin over the pH range from 2.9 to 6.2. The first and second cycles of CVs are shown in Fig. 2c and 2d. It can be seen in these figures that all the peak positions shift as the pH value is varied, suggesting that all the redox peaks are derived from proton-involved reactions. Furthermore, the dependence of E_p on pH value is also studied to reveal the details of the reaction mechanism.

As shown in Fig. 2e (a), the E_{pa} of phenacetin is proportional to the solution pH value in this range that is tested. This relationship can be expressed as:

$$E_{pa}(\mathrm{V}) = -0.0319\mathrm{pH} + 1.03 \quad (1)$$

Based on the Nernst equation, it can be concluded that two electrons and one proton are involved in the electrochemical reductions of phenacetin. This is a further indication of the formation of quinone-imine cation intermediate (I) in this reaction process (Scheme 1), followed by the hydrolysis of (I), which quickly produces the electroactive NAPQI.

The relationship between the E_{pc} of NAPQI and the solution pH value is shown in Fig. 2e (b), which can be expressed as:

$$E_{pc}(\mathrm{V}) = -0.063\mathrm{pH} + 0.75 \quad (2)$$

Here, the Nernst equation indicates that an equal number of electrons and proton are involved in this reduction reaction. Combining these results with those reported[3,7,25,26], it appears that the formation of acetaminophen can be confirmed to occur through a two electron and two proton reduction process (Scheme 1).

In the 2nd CV cycle (Fig. 2d), peak Ⅲ corres-

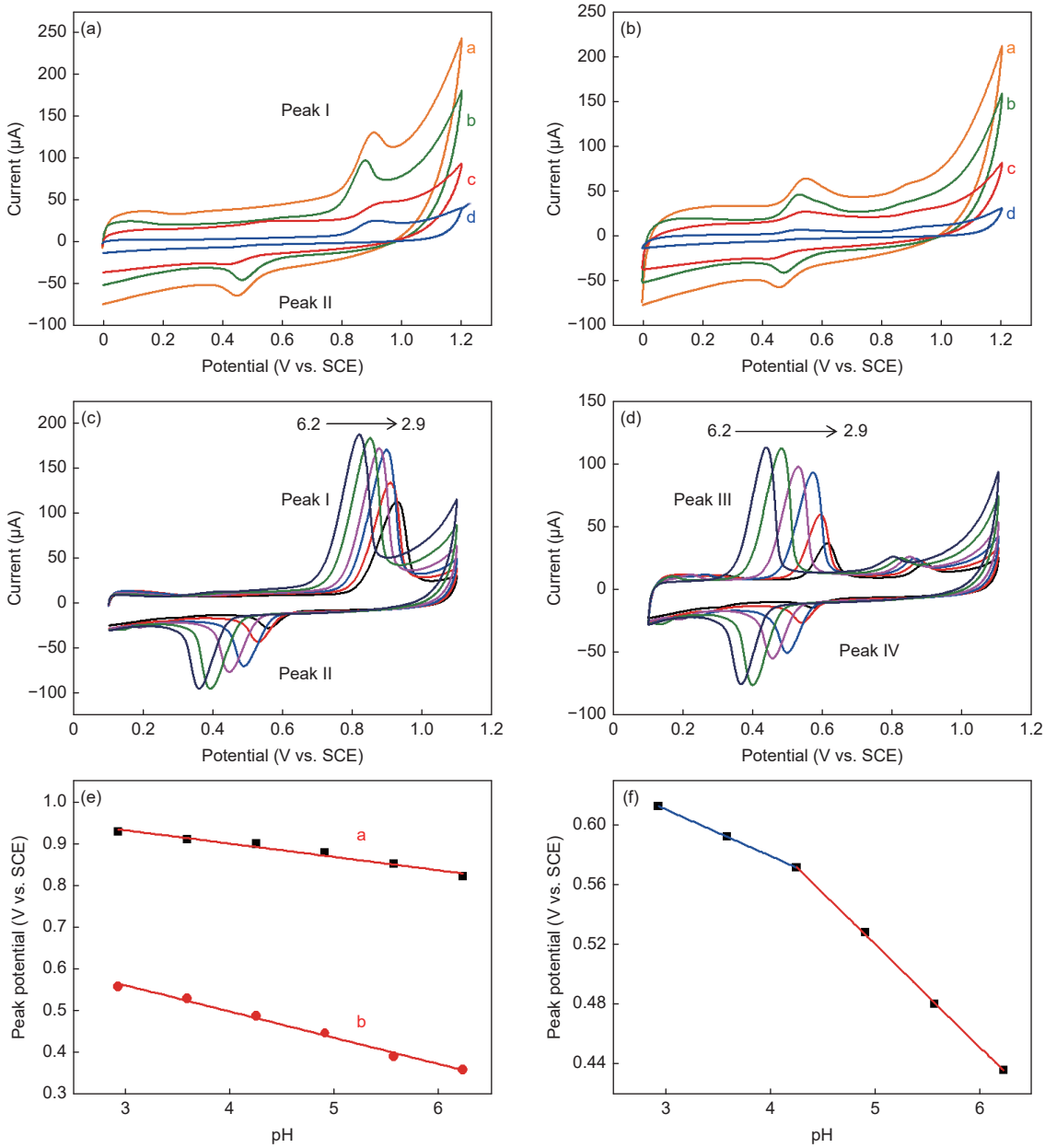


Fig. 2　CVs of phenacetin (0.05 mmol L^{-1}) on various modified electrodes (a) the 1st cycle and (b) the 2nd cycle (curve a: NGE-A, curve b: ERGO, cure c: NGE-U, curve d: NGE-N). CVs of phenacetin (0.1 mmol L^{-1}) on ERGO at different pH values (c) the 1st cycle and (d) the 2nd cycle. (e) Dependence of E_{pa} (phenacetin) and E_{pc} (NAPQI) on pH value. (f) dependence of E_{pa} (acetaminophen) on pH value at a scan rate of 100 mV s^{-1}.

ponds to the oxidation of acetaminophen. In this voltage range, the pH dependence of E_{pa} can be divided into two components, which can be expressed (Fig. 2f) as:

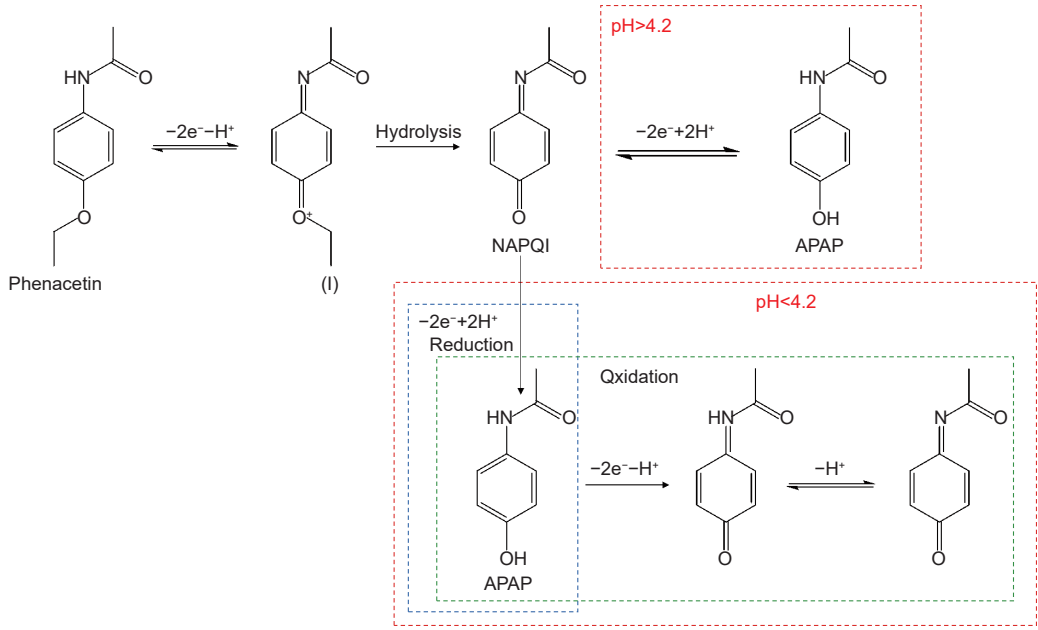
$$pH < 4.2 : E_{pa}(V) = -0.031pH + 0.70 \quad (3)$$

$$pH > 4.2 : E_{pa}(V) = -0.063pH + 0.86 \quad (4)$$

The various slopes of these plots are indicative of the different electrode reactions that occur at the various pH values. In the acidic condition, NAPQI is protonated and this protonated NAPQI is considered to be the main product of the electro-oxidization process[1,27]. Here, two electrons and one proton participate in this reaction. At pH values higher than 4.2, a 2-electrons/2-protons process is confirmed to occur as evidenced by the slope of 0.063, indicating a direct formation of NAPQI.

In the 2nd cycle (Fig. 2d), peak Ⅳ also corresponds to the reduction of NAPQI to acetaminophen as expressed by the equation (5).

$$E_{pc}(V) = -0.064pH + 0.76 \quad (5)$$



Scheme 1 Mechanism of phenacetin redox reactions.

This expression is quite close to Eq. 2, which suggests a similar reaction mechanism.

The dependence of the CV response on the scan rate (20-140 mV s^{-1}) was obtained for ERGO/GCE in CPS (pH=6.8). The 1st cycle of these CV curves is shown in Fig. 3a, where it can be seen that the peak currents increase with increasing the scan rate. The dependence of I_{pa} on the scan rate (v) is depicted in Figs. 3c and 3d. As shown, the I_{pa} of phenacetin is proportional to v with a good linearity, which indicates the presence of a surface controlled process (Fig. 3c). Similarly, the reduction of NAPQI is also found to be a surface diffusion-controlled process based on the I_p-v dependence (Fig. 3d).

The logI_p - log$v$ curves for each peak are shown in Figs. 3e and f, where the oxidation of phenacetin (Fig. 3e) can be expressed as:

$$\log I_{pa} = 0.62 \log v + 2.4 \quad (6)$$

The slopes of these plots (0.62) are between 1 and 0.5, which are the theoretic values for an adsorption-controlled process and diffusion-controlled process, respectively. This means that the determining steps for oxidation of phenacetin changes from the oxidation of surface adsorbed molecules before the reaction to the diffusion of reactants to the electrode surface after the reaction.

In the case of the logI_p - log$v$ for the redox of acetaminophen (Fig. 3f), all the slope values of the curves are higher than 1, which indicates the presence of a molecular adsorption-controlled process. It is concluded that the amount of acetaminophen at the electrode surface is beyond the saturated adsorption capacity. This may have been the result of the oxidation of the phenacetin, which suggests that more phenacetin molecules are adsorbed on the surface than acetaminophen.

The dependence of E_{pc} on ln$v$ is also shown in Fig. 3b, which can be expressed as:

$$E_{pc} = -0.0303 \ln v - 0.6314 \quad (7)$$

For an irreversible electrode process, E_{pc} can be defined by the following equation[28]:

$$E_{pc} = E^0 + (RT/\alpha nF) \ln\left(RTk^0/\alpha nF\right) - (RT/\alpha nF) \ln v$$

Where α is transfer coefficient, and is usually assumed to be 0.5 in a completely irreversible electrode process[29], v is the scan rate, n is the number of electrons transferred in the rate determining step, other symbols have their usual meanings. Accordingly, n is calculated to be 2, meaning that two electrons are involved in the rate determining step, indicating a direct oxidation from phenacetin to (I) (Scheme 1).

Based on these results, the reaction mechanism for the oxidation of phenacetin can be deduced as Scheme 1.

Fig. 4a shows the DPVs of the ERGO/GCE elec-

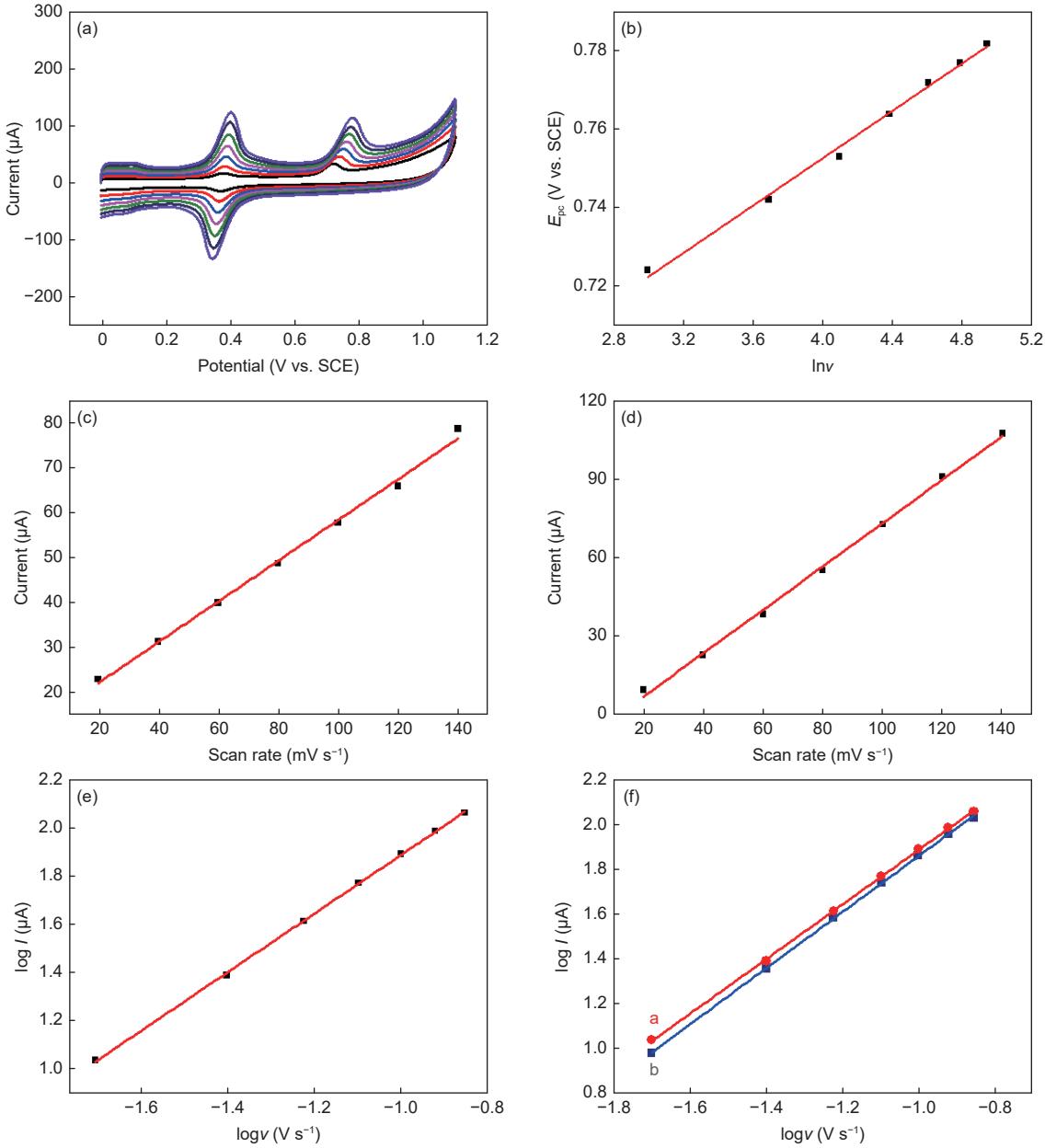


Fig. 3　(a) CVs of phenacetin (0.1 mmol L^{-1}) on ERGO at different scan rates (20-140 mV s^{-1}). (b) Dependence of E_{pc} on ln$v$. Dependence of the peak currents for (c) peak Ⅰ and (d) peak Ⅱ on the scan rate. (e) The relationship between log$I$ and log$v$ for phenacetin oxidation. (f) The relationship between log$I$ and logv for NAPQI reduction (red) and acetaminophen oxidation (black).

trode for various concentrations of phenacetin, where phenacetin was successively added to the solution. These results show that two well-defined oxidation peaks can be seen observed. But, there is only one oxidation peak ascribed to phenacetin because only the peak at ~0.7 V increases with successive additions of phenacetin, as shown in Fig. 4b. The relationship between the current response and concentration of phenacetin exhibits a good linear relationship with a stable peak potential. All these results indicate that the oxidation of phenacetin is not affected by the electrochemical synthesized acetaminophen. The relationship can be expressed as:

$$I_{pa} = 0.296c - 2.491$$

The detection limit (LOD) of phenacetin is calculated to be 0.91 μmol L^{-1} (S/N=3). Also, as proposed in the previous section, phenacetin is preferentially adsorbed over acetaminophen, suggesting that the current response derived from the oxidation of adsorbed phenacetin is not seriously affected by the presence of

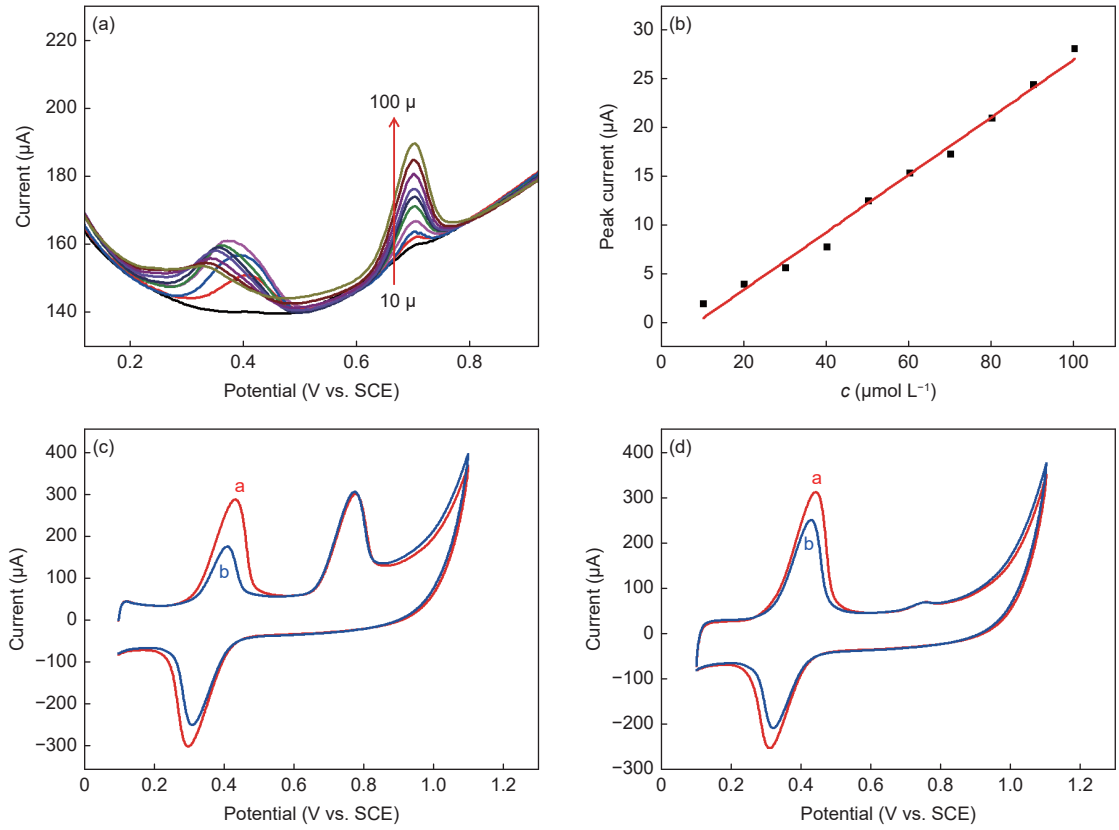


Fig. 4 (a) DPVs on ERGO with successive adding of phenacetin (10-100 μmol L^{-1}). (b) Dependence of the peak current on the phenacetin concentration. (c) The 1st CV cycle of 1 mmol L^{-1} phenacetin (curve b) and 1 mmol L^{-1} phenacetin + 1 mmol L^{-1} acetaminophen (curve a). (d) The 2nd CV cycle of 1 mmol L^{-1} phenacetin (curve b) and 1 mmol L^{-1} phenacetin + 1 mmol L^{-1} acetaminophen (curve a).

acetaminophen.

However, the response of acetaminophen does not simply increase with successive addition of phenacetin, which is in contrast to other literature reports[5,6]. The successive shift in the E_{pa} of acetaminophen suggests that a complicated electrode reaction have occurred. The decrease of I_{pa} (acetaminophen) at high phenacetin concentrations might have been resulted from competitive adsorption of the two. This means that a simultaneous determination of acetaminophen and phenacetin on graphene modified electrode is not possible. By contrast, the interference of acetaminophen on phenacetin detection is studied using CV analysis, and Fig. 4c is the 1st cycle of ERGO in PBS (pH=6.8) containing 0.1 mmol L^{-1} phenacetin (curve a) and 0.1 mmol L^{-1} phenacetin +0.1 mmol L^{-1} acetaminophen (curve b). It appears from these results that the acetaminophen does not adversely affect the response of phenacetin. In addition, in the 2nd cycle (Fig. 4d), the response of phenacetin maintains. Also, the anti-interference properties towards usual molecular were carried out by simultaneously determining phenacetin and interferents via DPV. 100-fold Cu^{2+}, Al^{3+} and 50-fold methanol, ethylene glycol, glucose, and ascorbic acid were added sequentially to PBS (pH=6.8) containing 0.01 mmol L^{-1} phenacetin. DPV results illustrat that all these species hardly cause interference, suggesting desirable phenacetin sensing performance (Table S1, ESI). All these results suggest good interference tolerance for phenacetin detection.

Usual reagents, such as Cu^{2+}, Al^{3+}, methanol, ethylene glycol, glucose, and ascorbic acid, show no obvious interference with the response of the ERGO for phenacetin. This suggests that the use of the ERGO for phenacetin sensors is reliable.

4 Conclusion

The electrochemical determination of phenacetin on an ERGO electrode was investigated. The results

suggest that ERGO has superior performance to several similar NGE electrodes. A desirable detection limit and good interference tolerance are obtained using the ERGO. Also, it is found that phenacetin interfers with the response of the ERGO for acetaminophen, suggesting that simultaneous detection of phenacetin and acetaminophen is not possible.

Acknowledgements

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