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Original scientific paper

Electroorganic synthesis of disulfonamide substituted *p*-benzoquinone by hydroquinone electrochemical oxidation

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Abstract

This study illustrates electrochemical behavior of hydroquinone and 4-amino-6-chlorobenzene-1,3-disulfonamide in the phosphate buffer solution evaluated by cyclic voltammetry. It was found that the peak of the hydroquinone oxidation potential in the presence of 4-amino-6-chlorobenzene-1,3-disulfonamide is shifted to more positive values compared to hydroquinone alone. Based on these results, the electrochemical synthesis of new disulfonamide substituted p-benzoquinone is proposed and carried out via electrochemical oxidation of hydroquinone in the presence of 4-amino-6-chlorobenzene-1,3-disulfonamide in the electrolytic cell. It has been concluded that hydroquinone is converted into disulfonamide substituted p-benzoquinone via an ECE mechanism. The successful electrochemical synthesis was conducted in the water/ethanol mixture under green conditions without any toxic reagents or solvents and with high atom economy.

Keywords

Cyclic voltammetry; electrochemical synthesis; hydroquinone; disulfonamide

Introduction

Electrochemistry provides a versatile way for electrosynthesis of biologically active intermediates and kinetic studies of different reagents that are of pharmaceutical importance [1]. Since electrochemical methods are simple and rapid, they are normally used to study electroactive compounds in pharmaceutical forms and physiological fluids. Quinones are classified in a large group of natural pigments that show excellent photochemical properties [2] and act as intermediates in a biosynthesis of important antibiotics [3]. Quinones exhibit biological activities such as antidiabetic [4] and are frequently used as charge transfer complexes [5]. Also, the change from hydroquinone to quinine plays an important role in redox processes occurring in living organisms. Quinones also act as electron–proton carriers for carrying oxygen in biochemical

reactions [6]. There are many works addressed to electro-oxidation of hydroquinone and its derivatives followed by the addition reaction with different nucleophiles such as 1-methylindole–triphenylphosphine-1,3-dimethylbarbituric acid [7-9]. Contrary to conventional organic synthetic methods that take place in organic solvents such as benzene, only few papers on the electrolytic synthesis of the sulfonamide derivatives have already been published.. This is somewhat strange because conventional organic synthetic reactions suffer from the necessity of heating, long reaction time and low atom economy [10,11].

Sulfonamides are synthetic drugs that have various therapeutic potential uses such as anti-metalloprotease [12], antibacterial, anti-diabetic [13], anti-carbonic anhydrase, diuretic [14], anti-thyroid, and antiviral activities [15].

Based on all these information, we believed that the synthesis of an organic compound with a structure of both sulfonamide and quinone groups would be useful from the perspective of pharmaceutical properties. This idea encouraged us to investigate the electrochemical oxidation of hydroquinone in the presence of disulfonamide as a nucleophile. The reaction is carried out in a single step with high atom economy under ambient conditions using a carbon anode.

Experimental

Apparatus and reagents

Cyclic voltammetry experiments were performed using an ampere-metric station model (Amel-433Analyser, Milano, Italy). The electrolytic cell with the glassy carbon working electrode was used. Ag/AgCl electrode as the reference, and a platinum wire as an auxiliary electrode were used. NMR ^{1}H and ^{13}C spectra were taken at 400 MHz Bruker. Infrared spectrum was taken on FT-IR-4100 from Jasco. All chemicals including 4-amino-6-chlorobenzene-1,3-disulfonamide and hydroquinone were purchased from Merck Laboratories and were analytical grade materials. Phosphate salt and solvents were all of pro-analysis quality and used without further purification. The water utilized in all studies was double-distilled and deionized.

Procedure

All voltammetric experiments were performed in water (phosphate buffer, c = 0.2 M)/ethanol (50/50 v/v) solution. Electroorganic synthesis of new substituted disulfonamide-para-benzoquinone was carried out in a single step, by using the electrolytic cell.

In a typical procedure, 70 ml of phosphate buffer solution (0.2 M, pH 8.0) was added to the water/ethanol mixture (35/65 v/v). This mixture contains 0.05 M of hydroquinone and 0.05 M of 4-amino-6-chlorobenzene-1,3-disulfonamide. The total solution was electrolyzed in a divided cell equipped with a zinc cathode, two carbon rods-anode and DC power supply set at 0.08 A. Current density was 6.413×10^{-3} A/cm^2.

The reaction was electrolyzed with constant stirring using a magnetic stirrer for two hours. The progress of the reaction was monitored by TLC plate. Then, evaporation of the solution was conducted and a brown colored product was obtained. This product was washed with ethanol and isolated at yield of 98 %. The product was characterized by spectroscopy (IR, ^{1}H NMR).

Results and discussion

Electrochemical behavior of hydroquinone

The cyclic voltammogram of glassy carbon electrode in a solution of hydroquinone (0.005 M) in a water (phosphate buffer, c = 0.2 M, pH 8.0)/ethanol mixture is shown in Figure 1. Anodic peak (A)

at 95 mV and a corresponding cathodic peak (B) at -57 mV can be clearly observed. These peaks correspond to the conversion of hydroquinone to *p*-benzoquinone and vice versa, proceeding by a quasi-reversible two electrons process.

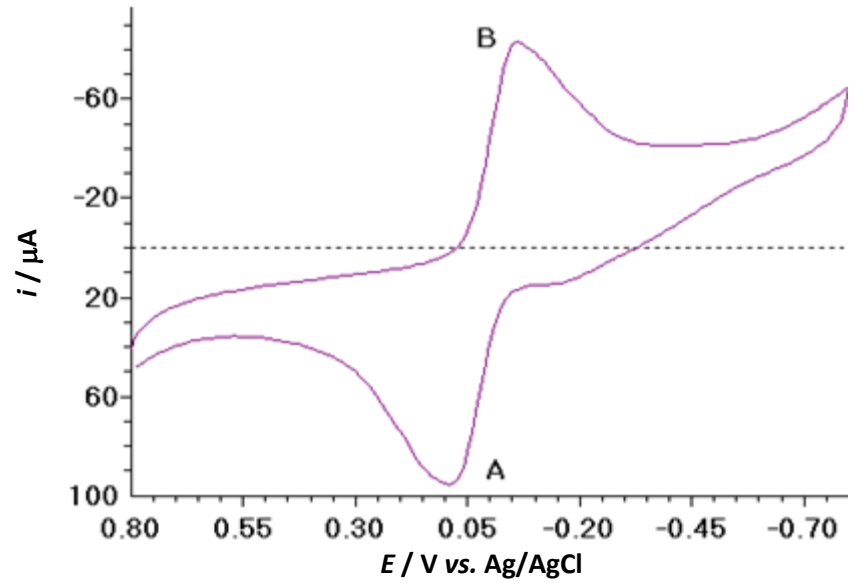


Figure 1. *Cyclic voltammogram hydroquinone (0.005M) on glassy carbon electrode. Scan rate: 100 mv* s^{-1} *Solvent water (phosphate buffer,* c *= 0.2M, pH 8.0)/ethanol.*

If, however, 1.0 mM solution of disulfonamide was put in the solution instead hydroquinone, not any peak was observed in the cyclic voltammogram recorded under same applied conditions.

The effect of pH on the voltammetric behavior of hydroquinone was monitored and it was seen that the peak (A) shifts to the negative potential by increasing pH value. Figure 2 represents the potential-pH diagram.

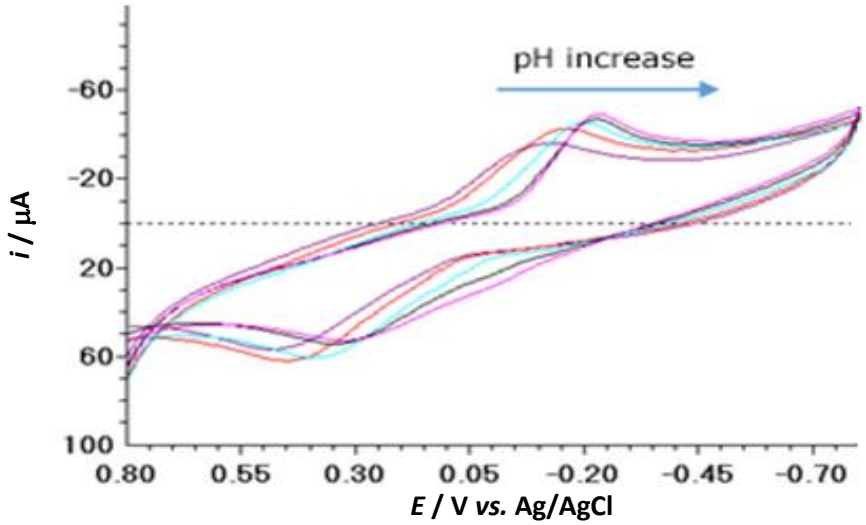


Figure 2. *Cyclic voltammogram of hydroquinone in phosphate buffer solution with various pH values on glassy carbon electrode. pH are 4.0,5.0,6.0,7.0 and 8.0, scan rate 100 mv* s^{-1}.

The anodic peak potential (E_{pA}) is given by [16]:

$$E_{pA} = E_{pA(pH\,0)} - 2.303\frac{mRT}{2F}\text{pH}$$

where *m* is the number of protons involved in the reaction, $E_{pA(pH\ 0)}$ is the anodic peak potential at (pH 0.0), while *R*, *T*, and *F* have their usual meanings. It is seen in Figure 3 that E_{pA} is shifted to less positive potentials with the slope of 62.2 mV/pH. This slope is in agreement with the theoretical slope (2.303 *mRT*/2*F*) of 59 mV/pH for *m* = 2. Based on this slope, it can be concluded that the electrode reaction is a two electron–two proton process. The ratio of the number of protons to electrons (*m*/*n*) indicates the slope of the potential-pH diagram. Upon increasing pH, the hydroxyl group dissociates to its anionic form. In other words, the proton of hydroxyl group does not participate in the electrochemical oxidation process. Hence, the potential-pH diagram is independent of the hydroxyl proton.

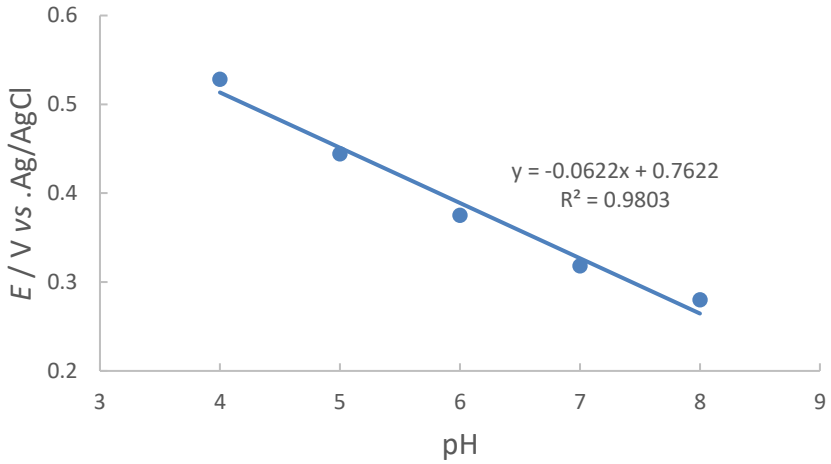


Figure 3. *Potential – pH diagram of hydroquinone*

Figure 4 shows cyclic voltammograms of hydroquinone with and without the presence of 4-amino-6-chlorobenzene-1,3-disulfonamide.

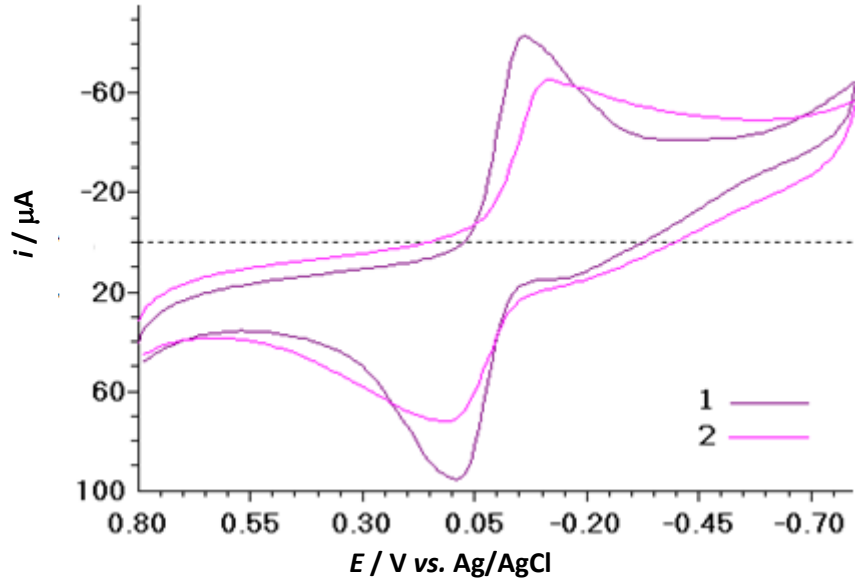


Figure 4. *Cyclic voltammograms of: (1) hydroquinone, (2) hydroquinone in the presence of 4-amino-6-chlorobenzene-1,3-disulfonamide on glassy carbon electrode, scan rate: 100 mv* s^{-1} *Solvent: water (phosphate buffer,c=0.2M,pH=8.0)/ethanol*

In the presence of sulfonamide, the current peak heights of hydroquinone are decreased and peak potentials are slightly shifted toward higher potentials, *i.e*. cathodic peak toward more

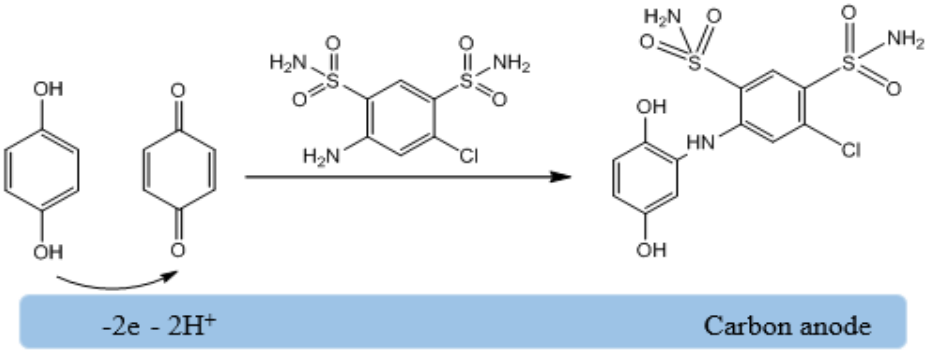
negative values while anodic peak shifted toward more positive values. Obviously, the presence of sulfonamide affects the reaction of hydroquinone at GC electrode, probably due to their chemical or physical association in the solution decreasing diffusion coefficient.

Electroorganic synthesis

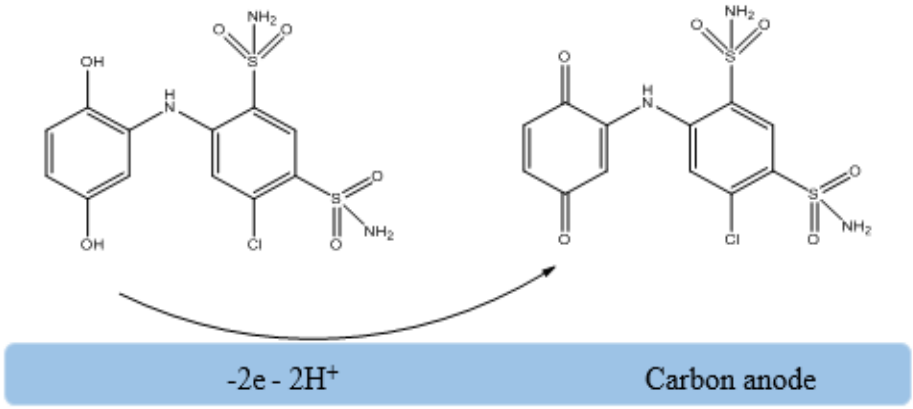
In order to investigate the possibility of synthetic utilization of the reaction, a preparative electrochemical oxidation of hydroquinone in the presence of 4-amino-6-chlorobenzen-1,3-disulfonamide was carried out in a divided cell containing 0.025 M of hydroquinone, 0.05 M of 4-amino-6-chlorobenzen-1,3-disulfonamide, and phosphate buffer solution (0.2 M, pH 8.0). The cell was equipped with a zinc cathode and two carbon rods anodes.

After 576 C (As) of electricity passed, the reaction was stopped and the resulting product isolated as described in Experimental section. The spectroscopic data of final product (IR, ^{1}H NMR, ^{13}C NMR) allowed us to propose the following pathway of the electrochemical oxidation of hydroquinone in the presence of 4-amino-6-chlorobenzen-1,3-disulfonamide:

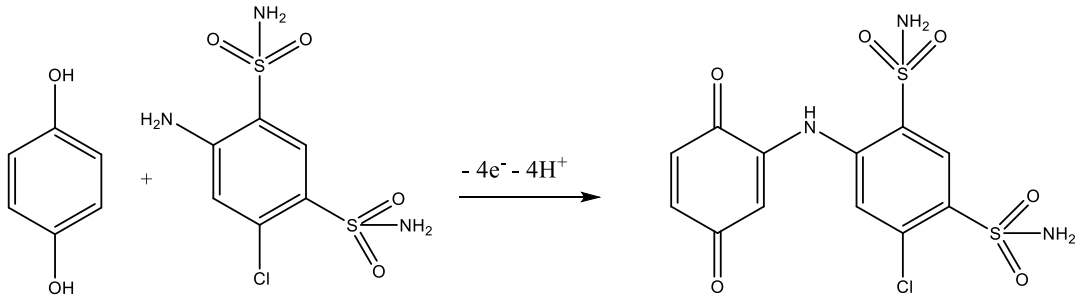
1. Firstly, hydroquinone oxidizes at the carbon anode by an electrochemical reaction into *p*-benzoquinone. Then, this product reacts with disulfonamide to produce a substituted hydroquinone. The reaction follows the Michael's addition mechanism.



2. Secondly, the substituted hydroquinone oxidizes into substituted *p*-benzoquinone in an electrooxidation reaction. This oxidation takes place at lower potentials than hydroquinone oxidation, what is due to the presence of the electron-donating amine functional group.



Hence, the overall reaction mechanism of the electrochemical synthesis followed the ECE mechanism and can be described as follows:



Spectral data:

^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.11(s,H, NH)- 7.3 (d, J=66Hz, 2H, quinone)- 6.9 (s, H,aromatic) - 6.6 (s, H, aromatic)- 3.3(s,2H, NH_2)- 3.7(s,2H, NH_2).

^{13}C NMR(DMSO-d6) δppm: 55.9, 104.3, 120.2, 129.6, 133.6,147.87, 158.13, 180.75,182 (C=O).

IR (KBr) v/cm^{-1}: 3407-3361 (NH_2), 3279 (NH), 1630 - 1552 (C=O), 1170 (S=O).

The atom economy was calculated for the synthesis substituted disulfonamide p-benzoquinone according to Eissen and coworkers (Eq. 1) [17]:

$$\text{Atom economy, \%} = \frac{\text{Atom mass (in desired product)}}{\text{Atom mass (in reactant)}} \times 100 \quad (1)$$

The calculated atom economy for the synthesis of substituted disulfonamide *p*-benzoquinone is 99.09 %. The high atom economy indicates that all atoms, except four hydrogen atoms from the starting materials are incorporated into the product.

The substituted disulfonamide p-benzoquinone compound was tested to evaluate its antibacterial activity by Agar-well diffusion method [18]. *Escherichia coli* (*E. coli* Gram-negative) was the bacteria used in this experiment. The created well was filled with 3 mg of substituted disulfonamide *p*-benzoquinone. The inhibition zone surrounding the wells (in millimeters) was measured to evaluate antibacterial activity. The results showed that *E. coli* has a little sensitivity to substituted disulfonamide *p*-benzoquinone. An outer membrane might be established and a set of multidrug resistance pumps in Gram-negative bacteria, such as *E.coli*, are quite effective barriers for antimicrobial compounds [19].

Conclusions

In summary, the pharmacological properties of disulfonamide and quinone encouraged us to synthesize a new compound containing disulfonamide and *p*-benzoquinone by electrochemical method. The results of cyclic voltammetric studies illustrated the ECE reaction mechanism. This mechanism started in electrooxidation reaction through hydroquinone oxidation to generate *p*-benzoquinone. Then this middle product was attacked by disulfonamide to produce the final product.

The synthesis of substituted disulfonamide *p*-benzoquinone was conducted in high atom economy and in accordance with the principles of green chemistry. These principles were the reaction in water/ethanol mixture instead of toxic solvents, running the reaction under room temperature, and the utilization of electrode as an electron source instead of the usage of any toxic reagents.

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