Estimation of Heterogeneous Rate Constants of Reaction of Electrochemically Generated *o*-Benzoquinones with Various Nucleophiles Containing Thiol Group

LIDA FOTOUHI,[1] ESMAIL TAMMARI,[2] SAMANEH ASADI,[1] MAJID M. HERAVI,[1] DAVOOD NEMATOLLAHI[3]

[1] *Department of Chemistry, School of Science, Alzahra University, Tehran, Iran*
[2] *Payame Noor University (PNU), Iran*
[3] *Faculty of Chemistry, Bu-Ali-Sina University, Hamadan, Iran*

Received 10 June 2008; revised 28 September 2008; accepted 2 November 2008

DOI 10.1002/kin.20402
Published online in Wiley InterScience (www.interscience.wiley.com).

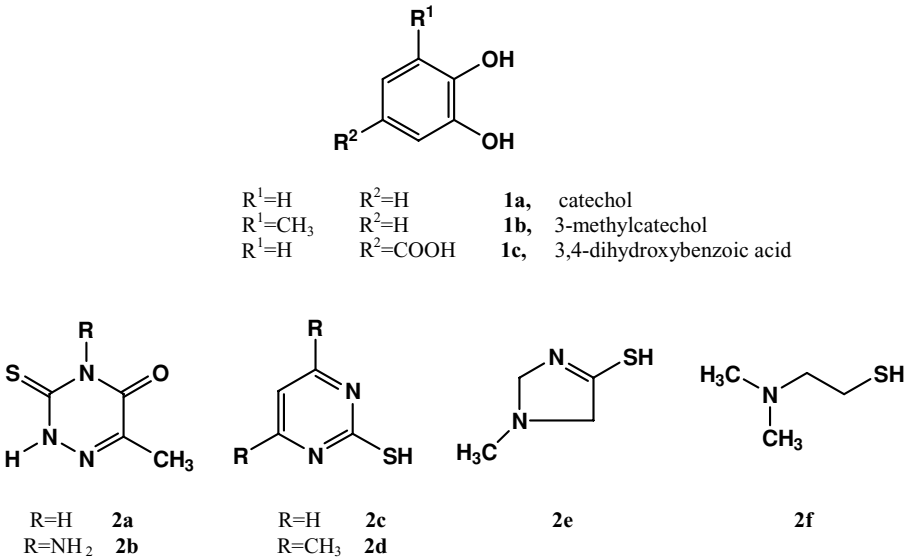
ABSTRACT: The reaction of *o*-benzoquinone derived by the oxidation of catechols (**1a–c**) with some nucleophiles containing thiol group (**2a–f**) has been studied in various conditions, such as pH, nucleophile concentration, and scan rate, using cyclic voltammetry. In various conditions, based on an EC electrochemical mechanism ("E" represents an electron transfer at the electrode surface and "C" represents a homogeneous chemical reaction), the observed homogeneous rate constants (k_{obs}) were estimated by comparison of the experimental cyclic voltammetric responses with the digital simulated results for each of the nucleophile. The results show that the magnitude of k_{obs} is dependent on the nature of the substituted group on the catechol ring and nucleophilicity of nucleophile. © 2009 Wiley Periodicals, Inc. Int J Chem Kinet 41: 426–431, 2009

INTRODUCTION

Catechol derivatives are a promising group of compounds worthwhile for further investigation, which may lead to the discovery of selective acting, biodegradable agrochemicals having high human,

Correspondence to: Lida Fotouhi; e-mail: lida_fotouhi@yahoo.com, lfotouhi@alzahra.ac.ir.

Contract grant sponsor: Research Council of Al-Zahra University.



Scheme 1

animal, and plant compatibility [1]. On the other hand, quinones are of considerable interest because many drugs such as doxorubicin, daunorubicin, and mitomycin C in cancer chemotherapy contain quinones [2], whereas various quinones have been found useful in industry [3]. Some of them also exhibit antitumor and antimalarial activities [4], and many of them are also involved in enzyme inhibition and DNA cross-linking [5].

Application of biological thiols as nucleophilic species in 1,4-Michael additions to electrogenerated *o*-quinones as protocols for the detection of these compounds is also reported [6,7]. Substitutions including thiol [8] and alkylthiol [9] derivatives have been carried out primarily at the 3-position of the 1,2,4-triazole ring. A large number of 1,2,4-triazole derivatives have been reported to possess central nervous system–depressant antibacterial [10], antifungal [11], antitumor [12], and insecticidal properties [13].

Some electrochemical techniques such as cyclic voltammetry (CV), using diagnostic criteria derived by Nicholson and Shain for various electrode mechanisms, have been used as a powerful independent route for quantitative characterization of complex electrode processes [14–16]. In addition, general treatment of the reaction mechanism is probably best carried out through digital simulation [17].

With due attention to our experiences [18–20], we thought that the kinetic study of reaction of electrogenerated *o*-benzoquinone with thionucleophiles would be of interest from the point of view of pharmaceutical properties. In our previous works [21–25], we have investigated the electrooxidation of some catechol derivatives (**1a–c**) in the presence of some side-chain thiol group nucleophiles (**2a–f**) in detail. In this work, the k_{obs} values of the reaction of *o*-benzoquinone derived from **1a–c** with **2a–f** (Scheme 1) have been estimated by digital simulation of CV at various experimental conditions, such as pH, scan rate, and nucleophile concentration.

EXPERIMENTAL

Apparatus

Cyclic voltammetry was performed using an Autolab PGSTATE12 (Eco Chemie, Utrecht, Netherlands). The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc (1.8-mm diameter) and platinum wire was used as the counter electrode (CE). The WE potentials were measured versus the 3 M KCl Ag/AgCl reference electrode (all electrodes were obtained from Metrohm, Herisau, Switzerland).

The homogeneous rate constants were estimated by analyzing the cyclic voltammetric responses using the simulation CVSIM software [26]. All experiments were carried out at room temperature.

Chemicals

Catechols were reagent-grade materials from Aldrich. All chemical reagents were of pro-analysis grade from Merck (Darmstadt, Germany) and Fluka (Milwaukee, WI, USA). These materials were used without further purification.

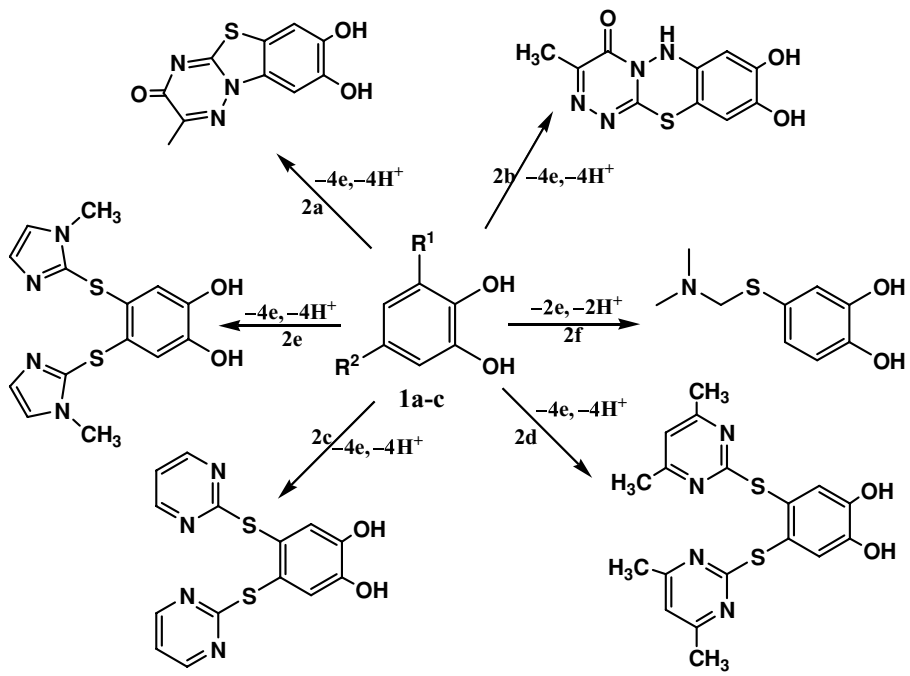
RESULTS AND DISCUSSION

Voltammetric Studies

Cyclic voltammogram of catechol (**1a**) in aqueous solution containing 0.2 M phosphate buffer (pH = 7.0) shows one anodic and the corresponding cathodic peak, which belongs to the transformation of catechol to *o*-benzoquinone and vice versa within a quasi-reversible two-electron process. In the presence of a nucleophile, the height of cathodic counterpart decreased, while the potential of anodic peak slightly shifted toward the less positive potential. Recording cyclic voltammogram of catechol in the presence of nucleophile at different scan rates shows a decreasing both peak current ratio (I_a/I_c) and current function ($I_a/\upsilon^{1/2}$) with an increasing scan rate, which is a clear indication of coupled chemical reaction via EC or ECEC mechanism. In our previous works [21–25], we have studied the electrooxidation of catechols in aqueous solutions in the presence of some nucleophiles containing thiol group and have shown that catechols undergo Michael addition with consumption 2- or 4-electrons per molecule of catechol (Scheme 2). As it is shown in Scheme 2, in the case of nucleophiles **2a** and **2b** generation of *o*-benzoquinone is followed by a 1,4-Michael addition of nucleophile to the quinone producing the adduct, which undergoes the abstraction of a second pair of electrons and cyclization via attack by the NH_2 group (ECEC mechanism). On the other hand, nucleophiles **2c** and **2d** show an ECEC mechanism via consumption of 4-electrons per catechol molecule without any cyclization. Finally in nucleophiles **2e** and **2f** when *o*-quinone is formed, it will be attacked by nucleophile to furnish catecholthioether via 2- or 4-electrons per catechol molecules (Scheme 2). However, all nucleophiles show similar 1,4-Michael addition EC mechanism at the first step in which the electrogenerated *o*-quinone as a Michael acceptor is attacked by the SH group. Herein, we wish to investigate a quantitative detailed study of the electrochemical oxidation of catechols in the presence of various thionucleophiles for finding any relationship between them. CV using diagnostic criteria derived by Nicholson and Shain [14–16] for various electrode mechanisms were used. To study the effect of the presence of an electron-donating and electron-withdrawing group in a reactive catechol ring site, electrochemical oxidation (**1a–c**) has been studied in the presence of some thionucleophiles (**2a–f**).

Kinetic Considerations

The simulation was carried out assuming semi-infinite one-dimensional diffusion and planar electrode geometry. The experimental parameters entered for digital simulation consisted of the following: $E_{start} = -0.3$ V (or -0.2 V), $E_{switch} = 0.6$ V (or 0.75 V), $t = 25°C$, and analytical concentration of catechol 1.0 mM. The transfer coefficients (α) were assumed to be 0.5 and



Scheme 2

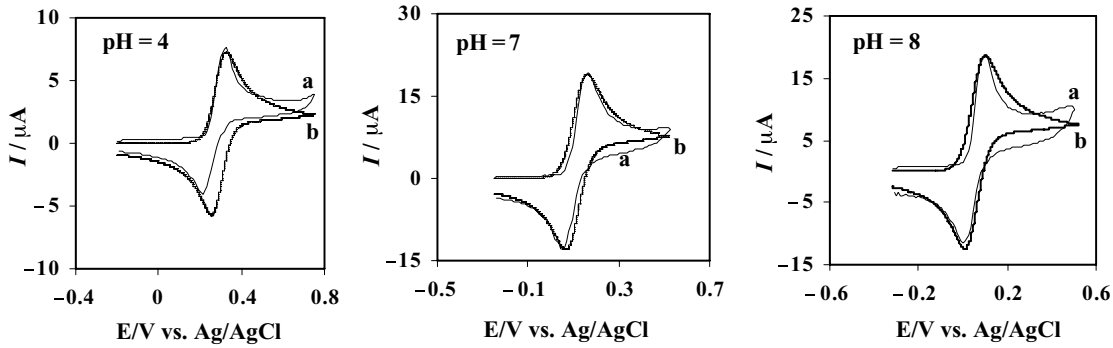


Figure 1 Typical cyclic voltammograms of 1 mM 3-methylcatechol (**1b**) and 1 mM **2b** at various pHs. (a) Experimental (dashed line); (b) simulated (solid line). Scan rates: 200 mV s^{-1}. WE: glassy carbon electrode.

the formal potentials were obtained experimentally as the midpoint potential between the anodic and cathodic peaks (E_{mid}). The heterogeneous rate constants (0.01 cm s^{-1}) for oxidation of catechols were estimated by use of an experimental working cure [27]. All parameters were kept constant throughout the fitting of the digitally simulated voltammogram to the experimental data. The parameter k_{obs} was allowed to change through the fitting processes. The observed homogeneous rate constants (k_{obs}/s^{-1}) of the reaction of *o*-benzoquinone with **2a–f** were estimated by comparison of the simulation results with experimental cyclic voltammograms at various pH, nucleophile concentration, and scan rates.

The Effect of pH

The schemes for the electrochemical oxidation of catechols (**1a–c**) in the presence of **2a–f** were proposed and tested by digital simulation for calculation of k_{obs} values. Typical experimental and simulated cyclic voltammograms of 3-methylcatechol (**1c**) in the presence of **2b** at various pHs are shown in Fig. 1. From the fitting of the digitally simulated voltammogram to the experimental data, the k_{obs} values were calculated. A typical Fig. 2 shows the calculated k_{obs} as a function of pH and constant scan rate and nucleophile concentration. As is shown in Fig. 2 by increasing pH, the k_{obs} values increased. Because at high pHs, the nucleophiles are in the deprotonated form, their nucleophilicity character is increased in the Michael addition of *o*-quinone derivatives. The other reason of increasing k_{obs} with pH is due to easier oxidation of catechol at basic pHs due to the participation of proton in the oxidation reaction of catechol to *o*-quinone.

$$R \leftrightarrow O + mH^+ + 2e$$

The anodic peak potential of catechol shifted to the negative potential by increasing pH. The formal potential for this reaction scheme is given by the following equation:

$$E^{0\prime} = E^0(pH_0) - (2.303\ RT/nF)\ pH$$

where E^0 (pH_0) is the formal potential of pH_0, R the gas constant, T the absolute temperature, and F the Faraday constant [17]. The plot of formal potential ($E^{0\prime}$) of catechol as a function of pH shows the slope of 0.061 mV pH^{-1}, which is in good agreement with the theoretical slope (2.303 RT/nF) of 59 mV pH^{-1} with $m = 2$.

The Effect of Nucleophile Concentration and Scan Rate

The simulation was also performed on the basis of EC mechanism at both various nucleophiles concentration and scan rates. It was found that the magnitude of k_{obs} is

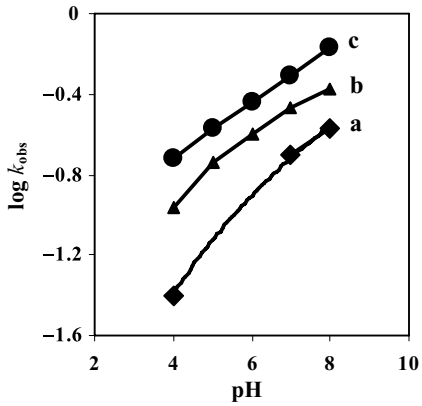


Figure 2 Plot of log k_{obs} for Michael addition of catechols (**1a–c**) as a function of pH for **2b** in the presence of (a) **1c**, (b) **1a**, (c) **1b**.

Table I The Averaged Values of Observed Homogeneous Rate Constants ($k_{obs}(s^{-1})$) for the Studied Catechols (**1a–c**) in the Presence of Different Concentrations of **2a–f** (0.10, 0.50, and 1.0 mM) and Various Scan Rates (25, 50, 100, 250, and 500 mV s^{-1})

Nucleophile	3-Methylcatechol	Catechol	3,4-Dihydroxybenzoic Acid
2a	0.14 (±0.02)	0.25 (±0.02)	0.48 (±0.02)
2b	0.21 (±0.03)	0.30 (±0.01)	0.58 (±0.01)
2c	0.40 (±0.02)	0.57 (±0.01)	0.78 (±0.06)
2d	0.53 (±0.02)	0.68 (±0.03)	0.89 (±0.05)
2e	0.67 (±0.02)	0.80 (±0.01)	0.98 (±0.02)
2f	0.93 (±0.02)	1.05 (±0.05)	1.42 (±0.04)

independent on both concentration of nucleophile and scan rate. Because k_{obs} is a thermodynamic parameter, it is obvious that it should be concentration independent. The averaged values of k_{obs} at various scan rates (25, 50, 100, 250, and 500 mV s^{-1}) and different nucleophile concentrations (0.10, 0.50, and 1.0 mM) are shown in Table I. On the other hand, k_{obs} values are dependent on the nature of the substituted group on the catechol ring. The presence of electron-donating group of methyl group on catechol ring causes a decrease in k_{obs}. In contrast, the presence of carboxylic group with electron-withdrawing character causes an increase in k_{obs}. The observed rate constants can be related with the Hammett ρ–σ parameters, where the Hammett equation is

$$\log k_i = \log k_0 + \rho\sigma$$

where k_i is the rate constant for substituted catechol, k_0 the rate constant for catechol, σ a constant characteristic of a given subsistent group [28], and ρ the slope of the log $k_0 - \sigma$ graph. The Hammett plot is shown in Fig. 3. The positive ρ values (e.g., 1.03, $r = 0.97$ for **2b**) mean that the transition state has a substantial negative charge because the reaction rate is increased significantly for electron-withdrawing substituents. This result is consistent with the attack of thiolate to the *o*-benzoquinone. The similar behavior was observed for other nucleophiles.

The order of observed homogeneous rate constants may also be explained according to the donating ability of substituted nucleophile. Nucleophile **2e** shows the higher value of k_{obs}, and then presence of electron-donating groups such as NH_2 or methyl on nucleophile causes an increase in k_{obs}. The order of k_{obs} for various nucleophiles is **2f** > **2e** > **2d** > **2c** > **2b** > **2a**.

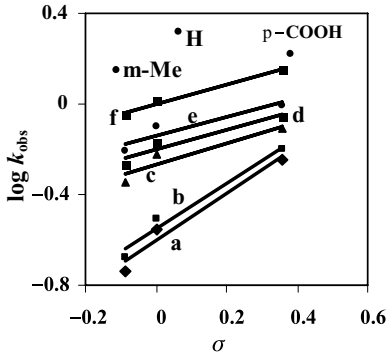


Figure 3 Hammett ρ–σ plot for catechols (**1a–c**) in the presence of (a) **2a**, (b) **2b**, (c) **2c**, (d) **2d**, (e) **2e**, and (f) **2f**.

CONCLUSIONS

The results of this work show the kinetics of the reactions of electrochemically generated *o*-benzoquinone, with some thionucleophils by the cyclic voltammetric technique and the simulation of obtained voltammograms performed under EC mechanism. There is a good agreement between the simulated voltammograms with those obtained experimentally. The effects of scan rate, nucleophile concentration, and pH on the oxidation pathway and the observed homogeneous rate constants have been discussed. In addition, the effects of the substituted groups on the catechol ring in k_{obs} (Hammett plot) have been studied.

BIBLIOGRAPHY

1. AMICBASE-EssOil. Database on Natural Antimicrobials, Review Science; AMICBASE-EssOil: Zirndorf, Germany, 2002.
2. Blum, R. H.; Carter, S. K. Ann Int Med 1974, 80, 249.
3. Kaleem, K.; Chertok, F.; Erhan, S. Prog Org Coating 1987, 15, 63.
4. Huang, Z. D.; Chen, Y. N.; Menon, K.; Teicher, B. A. J Med Chem 1993, 36, 1797.
5. Bittner, S.; Meenakshi, C.; Temtsin, G. Tetrahedron 2001, 57, 7423.
6. Lawrence, N. C.; Davis, J.; Compton, R. G. Talanta 2001, 53, 1089.

7. Huang, T. H.; Kuwana, T.; Warsinke, A. Biosens Bioelectron 2002, 17, 1107.
8. Hiremath, S. P.; Biradar, J. S.; Kuradi, S. M. J Indian Chem Soc 1984, 61, 74.
9. Ismail, M.; Yousif, M. Y.; Metwally, M. A. J Indian Chem 1984, 23B, 489.
10. Goswami, B. N.; Kataky, J. C. S.; Baruah, J. N. J Heterocycl Chem 1984, 21, 1225.
11. Heeres, J.; Backx, L. J. J Med Chem 1984, 27, 894.
12. Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. J Med Chem 1993, 36, 1090.
13. Wamhoff, H. Comprehensive Hetrocyclic Chemistry; Katritzky, A. R., Rees, C. W. (Eds.); Pergamon: Oxford, 1984; vol. 5, pp. 669–732.
14. Nicholson, R. S.; Shain, I. Anal Chem 1964, 36, 706.
15. Nicholson, R. S.; Shain, I. Anal Chem 1965, 37, 178.
16. Nicholson, R. S. Anal Chem 1965, 37, 1351.
17. Bard, A. J.; Faulkner, L. R. Electrochemical Methods, 2nd ed. Wiley: New York, 2001; p. 511.
18. Nematollahi, D.; Goodarzi, H. J Org Chem 2002, 67, 5036.
19. Nematollahi, D.; Ardakani, M. M.; Shekarlab, N. Int J Chem Kinet 2007, 39, 605.
20. Afkhami, A.; Nematollahi, D.; Khalafi, L.; Rafiee, M. Int J Chem Kinet 2005, 37, 17.
21. Fotouhi, L.; Mosavi, M.; Heravi, M. M.; Nematollahi, D. Tetrahedron Lett 2006, 47, 8553.
22. Fotouhi, L.; Nematollahi, D.; Heravi, M. M.; Tammari, E. Tetrahedron Lett 2006, 47, 1713.
23. Fotouhi, L.; Asadi, S.; Tammari, E.; Heravi, M. M.; Nematollahi, D. J Iran Chem Soc 2008, 5, 712.
24. Fotouhi, L.; Nematollahi, D.; Heravi, M. M. J Chin Chem Soc 2007, 54, 1163.
25. Fotouhi, L.; Taghavi Kiani, S.; Heravi, M. M.; Nematollahi, D. Int J Chem Kinet 2007, 39, 340.
26. Gosser, D. K. Cyclic Voltammetry: Simulation and Analysis of Reaction Mechanisms; VCH: New York, 1993.
27. Greef, R.; Peat, R.; Peter, L. M.; Pletcher, D.; Robinson, J. Instrumental Methods in Electrochemistry; Ellis Horwood Limited: New York, 1990; p. 189.
28. Hansch, C.; Leo, A.; Taft, R. W. Chem Rev 1991, 91, 165.