An efficient electrochemical synthesis of diamino-*o*-benzoquinone: Mechanistic and kinetic evaluation of the reaction of azide ion with *o*-benzoquinone†

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An efficient method for the synthesis of diamino-*o*-benzoquinone based on the Michael reaction of electrochemically generated *o*-benzoquinone with azide ion is described, as well as an estimation of the homogeneous rate constant (k_{obs}) of the reaction of *o*-benzoquinone with azide ion by the digital-simulation method.

Amino derivatives of quinones, important building blocks in the synthesis of a variety of natural products, medicinal compounds[1] with antitumor and antimalarial activities[2] are usually prepared by alternative, multistep synthetic pathways.[1,3] Also, the *ortho*-benzoquinone derivatives have been studied to a lesser extent than the *para*-benzoquinone derivatives because they are generally more difficult to prepare in even moderate yields.[2b,4]

We have a long-standing interest in the study of Michael additions to quinones and their use in the synthesis of compounds with natural patterns and of biological interest.[5] The obvious need for a convenient and high yielding synthetic method for the preparation of *ortho*-aminoquinones has prompted us to investigate the electrochemical oxidation of catechol in the presence of azide ion. We now report a new synthetic strategy involving the electro-oxidation of catechol to reach 4,5-diamino-*o*-benzoquinone in a single step with an environmentally friendly reagentless method in aqueous solution with high atom economy in ambient conditions in an undivided cell using a graphite electrode. Furthermore the observed homogeneous rate constant (k_{obs}) of the intramolecular reaction of *o*-benzoquinone with azide ions has been estimated by the digital simulation of the cyclic voltammograms.

The cyclic voltammogram of a 1 mM solution of catechol (**1**) in aqueous solution containing 0.2 M phosphate buffer (pH 6.5) is shown in Fig. 1 (curve a). The voltammograms show one anodic (A_1) and a corresponding cathodic peak (C_1), which corresponds to the transformation of catechol (**1**) to *o*-benzoquinone (**2**) and *vice-versa* within a quasi-reversible two-electron process. A peak

current ratio (I_{pC1}/I_{pA1}) of nearly unity, which can be considered as a criterion for the stability of *o*-benzoquinone (**2**), produced at the surface of the electrode under the experimental conditions.[5]

The oxidation of catechol (**1**) in the presence of azide ion as a nucleophile was studied in some detail. Fig. 1 (curve b) shows the cyclic voltammogram obtained for a 1 mM solution of **1** in the presence of 5 mM azide ion in aqueous solution containing 0.2 M phosphate buffer (pH 6.5). The voltammogram exhibits one anodic peak A_1 and four cathodic peaks ("$C_1 + C_2$", C_3 and C_4). These peaks are related to the reduction of intermediates **2**, **5**$_{ox}$ (counterpart of **5**), **4** and **6** respectively. The second cyclic voltammogram shows that, parallel to the decrease in current of A_1 and the shift of its potential in a positive direction, three new anodic peaks (A_2, A_3 and A_4) appear at less positive potentials (Fig. 1 (curve c)). These new peaks are related to electro-oxidation of intermediates **5**, **4**$_{red}$ and **6**$_{red}$ respectively. Intermediates, **4**$_{red}$ and **6**$_{red}$ are counterparts of **4** and **6** respectively. The positive shift of the A_1 peak in the presence of azide ion is probably due to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain extent the performance of the electrode process. Also, it is seen that proportional to the augmentation of the potential sweep rate, parallel to the increase in height of the C_1 the height of C_2, C_3 and C_4 decreases. A similar situation is observed when the azide ion to **1** concentration ratio is decreased. A plot of peak current ratio (I_{pA1}/I_{pC1}) *versus* logarithm of scan rate for a mixture of catechol (**1**) and azide ion, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates,

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† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR, FT-IR, MS of **8a** and cyclic voltammograms of the electrooxidation of catechol in the presence of azide at various pH and various scan rates. See DOI: 10.1039/b612224h
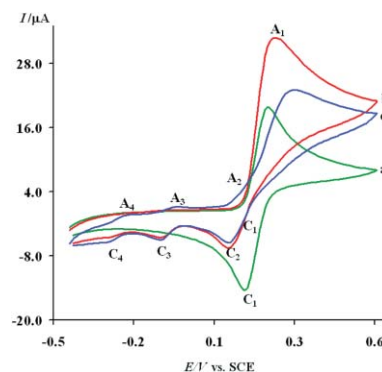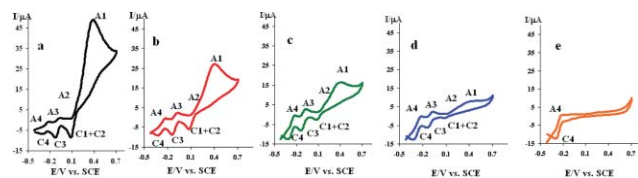
Fig. 1 Cyclic voltammograms of 1 mM catechol: (a) in the absence of azide ion, (b) in the presence of 5 mM of azide ion, the first cycle and (c) second cycle, at a glassy carbon electrode, in aqueous solution containing 0.2 M phosphate buffer (pH 6.5). Scan rate, 50 mV s^{-1}. $t = 25 \pm 1$ °C.

Fig. 2 Cyclic voltammograms of 0.15 mM catechol in the presence of 0.75 mM of sodium azide, at a glassy carbon electrode during controlled potential coulometry at 0.40 V (*versus* SCE). (a) to (e) in the course of coulometry at 0, 30, 80, 200 and 400 min. Other conditions are the same as reported in Fig. 1.

confirms the reactivity of **2** towards azide ion. On the other hand, the current function for the A_1 peak ($I_{pA1}/v^{1/2}$) changes on increasing the scan rate.

Controlled-potential coulometry was performed in aqueous solution containing 0.15 mM of **1** and 0.75 mM of azide ion in a divided cell at 0.40 V (*versus* SCE). Monitoring of the progress of the electrolysis was carried out by cyclic voltammetry (Fig. 2). During coulometry, in parallel with the decrease in height of anodic peak A_1 and its cathodic counterpart (C_1), other anodic and cathodic peaks appear and the height of them increases. At the end of the coulometry all of the anodic and cathodic peaks disappear and only anodic and cathodic peaks A_4 and C_4 remain. The residual A_4 and C_4 peaks are related to the redox reactions of **6**. The anodic peak A_1 disappears when the charge consumption becomes about 4.7 e^- per molecule of **1**. These observations allow us to propose the pathway in Scheme 1 for the electrochemical oxidation of **1** in the presence of azide ion.

According to our results, it seems that the Michael addition reaction of azide ion to *o*-benzoquinone (**2**) (eqn (3)) leads to intermediate **3**. In the next step, azidocatechol **3**, *via* an overall intramolecular oxidation–reduction reaction,[6] converts to amino-*o*-benzoquinone **4** (eqn (4)). Next Michael addition and
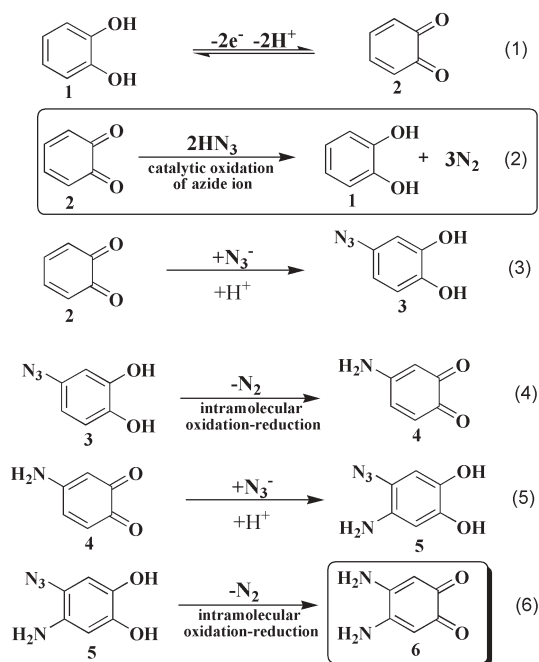
Scheme 1
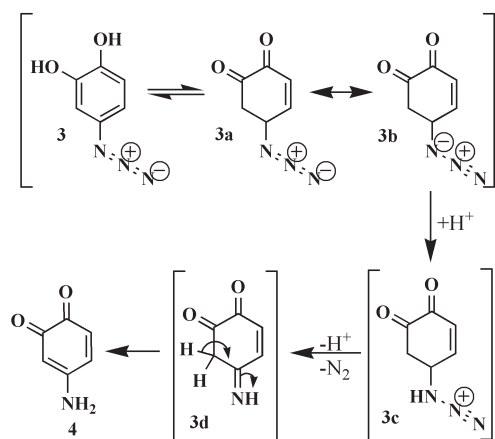
Scheme 2

intramolecular oxidation–reduction reactions (eqn (5) and (6)) converts **4** to diamino-*o*-benzoquinone **6** as the final product (68% isolated yield).‡ Formation of amino-*o*-benzoquinone (**4**) or diamino-*o*-benzoquinone (**6**) under intramolecular oxidation–reduction reaction conditions can be rationalized as shown in Scheme 2. According to this mechanism, **3b** is converted to imino intermediate **3d** by loss of N_2. Compound **3d** is then readily transformed to the stable tautomeric form of 4-amino-*o*-benzo-quinone (**4**).[6a]

In order to elucidate more of the reaction mechanism and also to determination of the optimal conditions for the addition of azide ion to catechol, we studied the electrochemical oxidation of catechol (**1**) in the presence of azide ion at various pHs. The results indicate an increase in anodic peak current (A_1) against a decrease in current of cathodic peaks (C_2, C_3 and C_4) with decreasing pH. Also, in controlled potential coulometry the number of consumed electrons increases with decreasing pH. These observations allow us to propose a homogeneous catalytic pathway in Scheme 1, eqn (2) for the electrochemical oxidation of **1** in the presence of azide ion in acidic medium.[7].§ This type of reaction, previously reported by Couladouros and co-workers in the reaction of hydrozoic acid with naphthoquinone,[6a] is confirmed by other typical voltammetric tests. This reaction is also responsible for increasing the number of consumed electrons from 2 to 4.7 e^- per molecule of **1** (Scheme 1). According to our results, the rate of formation of the azido adduct **3** increases proportionally with the increase in pH. In basic solutions, the peak current ratio (I_{pC1}/I_{pA1}) of catechol (in the absence of nucleophiles) is significantly less than unity and dramatically decreases with increasing pH. These can be related to the coupling of anionic or dianionic forms of catechols with *o*-benzoquinone (dimerization reaction).[8] The rate of this reaction is pH dependent and increases with increasing pH. Therefore, in basic solutions the cathodic peaks C_2, C_3 and C_4 have been removed from the cyclic voltammogram of catechol in the presence of azide ion. Because of the decrease in the rate of electron transfer reaction between azide ion and *o*-benzoquinone (**2**) (Scheme 1, eqn (2)) on the one hand and the decrease in the rate of homogeneous dimerization reaction on the other hand, pH 5.0–6.5 has been selected as a suitable medium for the electrochemical study and synthesis of diamino-*o*-benzoquinone (**6**).

Constant-current coulometry was performed in an aqueous solution containing 0.25 mM of **1** and 1.25 mM of azide ion in an
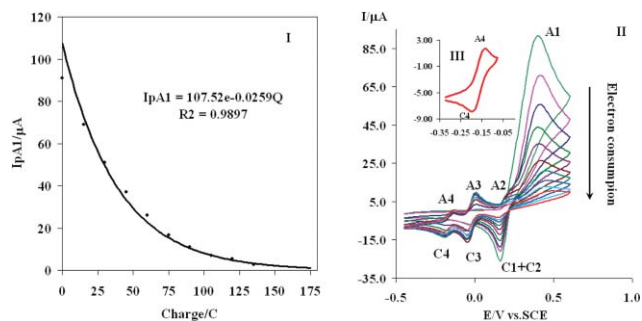
Fig. 3 (I) Variation of peak current I_{pA1} *versus* charge consumed during constant-current coulometry. (II) Cyclic voltammograms of 0.25 mM catechol (**1**) in the presence of 1.25 mM sodium azide during constant-current coulometry. (III) Cyclic voltammogram of final product. In aqueous solution containing 0.20 M acetate buffer (pH 5.0). Other conditions are the same as reported in Fig. 1.
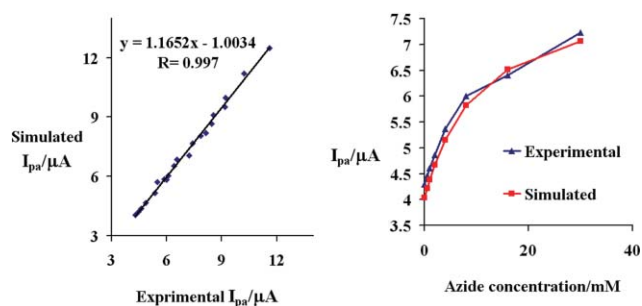

Fig. 4 (a) The correlation between simulated and experimental results. (b) Variation of peak current I_{pA1} *versus* azide ion concentration.

undivided cell, under current density 2 mA cm^{-2}. Monitoring of the progress of the electrolysis was performed by cyclic voltammetry (Fig. 3). The results are the same as those reported for the controlled potential coulometry. A characteristic feature of the electrolysis is the use of low current density: the current efficiency and yield of product decrease with increasing current density. These observations can be explained by the occurrence of some back reactions, such as the reduction of *o*-benzoquinones **2**, **4** or **6** on the cathode and side reactions such as oxidation of the nucleophile and/or solvent during constant current electrolysis in an undivided cell. In this work to improve the applicability of the procedure, the electrochemical synthesis of **6** was also performed by means of constant current electrolysis (*ca.* 2 mA cm^{-2}).¶

The observed homogeneous rate constant (k_{obs}/M^{-1} s^{-1}) of the reaction of *o*-benzoquinone (**2**) with azide ion has been estimated by comparison of the simulation results[9] with the experimental cyclic voltammograms. The simulation was performed based on an ECE electrochemical mechanism. The procedure is performed based on achieving the best fit between simulated and experimental cyclic voltammograms. This method is applied to a variety of scan rates and nucleophile concentrations. The estimated value for k_{obs} is 35 $\pm$ 3 M^{-1} s^{-1} and k_f/k_b is 150 $\pm$ 10. A correlation of 99.7% between oxidation peak current (I_{pA1}) of two sets of experimental and related simulated cyclic voltammograms over a variety of scan rates and azide ion concentrations, and also close correspondence

of experimental and related simulated results (Fig. 4), confirm the validity of the estimated k_{obs}.

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Notes and references

1 (*a*) E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297–386; (*b*) D. L. Boger, S. R. Duff, J. S. Panek and M. J. Yasuda, *J. Org. Chem.*, 1985, **50**, 5782–5789; (*c*) D. L. Boger, S. R. Duff, J. S. Panek and M. J. Yasuda, *J. Org. Chem.*, 1985, **50**, 5790–5795; (*d*) J. Renault, S. Giorgi-Renault, M. Baron, P. Mailliet, C. Paoletti, S. Cros and E. J. Voisin, *J. Med. Chem.*, 1983, **26**, 1715–1719; (*e*) A. S. Kende and F. H. Ebetino, *Tetrahedron Lett.*, 1984, **25**, 923–926; (*f*) R. H. Thomson, *Naturally Occurring Quinones*, Academic Press, New York, 2nd edn, 1971; (*g*) H. Nagaoka and Y. Kishi, *Tetrahedron*, 1981, **37**, 3873–3888; (*h*) G. Lancini and W. Zanichelli, in *Antibiotics*, ed. D. Perlman, Academic Press, New York, 1971, pp. 531–600.
2 (*a*) T. S. Lin, S. P. Xu, L. Y. Zhu, A. Divo and A. Sartorelli, *J. Med. Chem.*, 1991, **34**, 1634–1639; (*b*) Z. D. Huang, Y. N. Chen, K. Menon and B. A. Teicher, *J. Med. Chem.*, 1993, **36**, 1797–1801.
3 H. W. Moore, H. R. Shelden, D. W. Deters and R. J. Wikholn, *J. Am. Chem. Soc.*, 1970, **92**, 1675–168.
4 C. Kashima, A. Tomotake and Y. Omote, *J. Org. Chem.*, 1987, **52**, 5616–5621.
5 (*a*) D. Nematollahi and E. Tammari, *J. Org. Chem.*, 2005, **70**, 7769–7772; (*b*) D. Nematollahi and M. Rafiee, *Green Chem.*, 2005, **7**, 638–644; (*c*) D. Nematollahi, D. Habbibi, M. Rahmati and M. Rafiee, *J. Org. Chem.*, 2004, **69**, 2637–2640; (*d*) D. Nematollahi and H. Goodarzi, *J. Org. Chem.*, 2002, **67**, 5036–5039; (*e*) S. S. Hosseiny Davarani, D. Nematollahi, N. Mashkouri Najafi, L. Masoumi and S. Ramyar, *J. Org. Chem.*, 2006, **71**, 2139–2142; (*f*) D. Nematollahi, M. S. Workentin and E. Tammari, *Chem. Commun.*, 2006, 1631–1633.
6 (*a*) E. A. Couladouros, Z. F. Plyta and S. A. Haroutounian, *J. Org. Chem.*, 1997, **62**, 6–10; (*b*) L. F. Fieser and J. L. Hartwell, *J. Am. Chem. Soc.*, 1935, **57**, 1482–1484; (*c*) K. A. Parker and M. E. Sworin, *J. Org. Chem.*, 1981, **46**, 3218–3223; (*d*) A. R. Forrester, A. S. Ingram, I. C. John and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1115–1120.
7 A. J. Bard and L. R. Faulkner, *Electrochemical Methods*, Wiley, New York, 2nd edn, 2001, p. 501.
8 (*a*) D. Nematollahi, M. Rafiee and A. Samadi-Maybodi, *Electrochim. Acta*, 2004, **49**, 2495–2502; (*b*) M. D. Ryan, A. Yueh and C. Wen-Yu, *J. Electrochem. Soc.*, 1980, **127**, 1489–1495.
9 M. Rudolph, *J. Electroanal. Chem.*, 2002, **529**, 97–108. Also, see: http://www.digielch.de/.
10 (*a*) A. Dalmia, S. Wasmus, R. F. Savinell and C. C. Liu, *J. Electrochem. Soc.*, 1996, **143**, 556–560; (*b*) P. Bandyopadhyay, B. B. Dhar, J. Bhattacharyya and S. Mukhopadhyay, *Eur. J. Inorg. Chem.*, 2003, **24**, 4308–4312.