Electrochemical synthesis of 3-amino-4-hydroxybenzoic acid in aqueous base

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The electrochemical reduction of 3-nitro-4-hydroxybenzoic acid (1) in basic medium at a copper cathode is a facile process and has been scaled to produce over 35 kg of the corresponding aniline (2) isolated as the HCl salt. The trifunctional compound is an important intermediate for the synthesis of polybenzoxazoles and can be self-polymerized to produce an a–b type polymer.
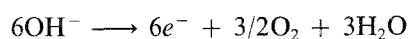
1. Introduction

The electrochemical reduction of 3-nitro-4-hydroxybenzoic acid (1) to the corresponding aniline (2) is a potentially important process since the trifunctional compound is an important intermediate for the synthesis of a polybenzoxazole via self-polymerization. Process details outside the scope of this report suggest that the reduction should be performed in basic medium (thus the structures in Scheme 1 actually exist as the disodium salts).

Cathodic reaction

Anodic reaction

$$6OH^- \longrightarrow 6e^- + 3/2 O_2 + 3H_2O$$
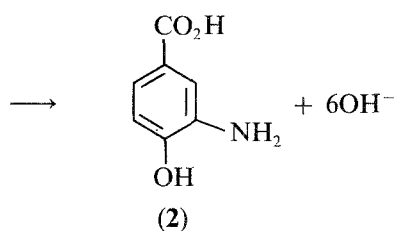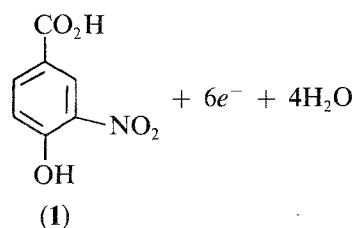
Scheme 1.

It is generally accepted that reduction of nitroaromatics in neutral to basic media results in coupling of two intermediates to form N–N coupled products, whereas in acidic media reduction to the aniline is usually observed. Reduction in basic media proceeds through the nitroso and then hydroxylamine intermediate which can couple to form azoxy and, ultimately, azo

or hydrazobenzenes (e.g. [1, 2]). Hydrazobenzenes generally cannot be electrolytically reduced to the aniline in base. Therefore, dimerization in an electrolytic reduction results in an irreversible loss of chemical yield of the aniline.

There are a few examples of the electrolytic reduction of nitroaromatics to the corresponding anilines in basic media (e.g. [3–7]). References [3–6] indicate a facile reduction of o-nitrophenol to o-aminophenol in base. Brown and Warner [3, 4] studied the relationships of yield vs current density and electrode material and concluded that copper is a suitable cathode only at low current density (about $20\,mA\,cm^{-2}$) while lead and zinc were the cathodes of choice at higher current densities. This is in contrast with our findings which indicate that copper is probably the best overall cathode at all current densities with the added features of minimal corrosion, low cost and high current efficiency.

Bradt and Hart [7] have shown that 3-nitro-4-hydroxytoluene can be converted to the aniline in sodium carbonate at a tin cathode in high yield.

Belot et al. [8] indicate that copper is not suitable for the reduction of unsubstituted nitrobenzene to aniline in basic media which essentially agrees with our findings. These authors claim that a specially activated Devarda copper cathode can be used for this conversion at low current density ($8\,mA\,cm^{-2}$). This is a unique finding which may be significant if their electrode is robust and the lengthy preparation not too uneconomical.

Honda et al. [9] state that p-nitrosalicylic acid (2-hydroxy-4-nitrobenzoic acid) cannot be converted into the aniline under basic conditions.

We have investigated several electrochemical parameters and determined to some extent which classes of compounds are amenable to conversion to the aniline in basic media [10]. In summary, we have found that several cathode materials including copper, carbon, platinum, nickel and stainless steel are suitable for this chemistry given a specific substitution

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pattern on the organic. Copper and carbon appear to be the best choices for the cathode material. Yield, conversion and current efficiency are not strongly dependent on the typical variables (temperature, current density and electrolyte). The functionality and positional isomerism are the most important factors in the determination of the pathway of reduction of nitroaromatics. For 10 classes of compounds studied, significant yields (> 50%) of anilines in base are obtained when substitution by -OH, -OEt, -OMe or -CH$_3$ is ortho or para to the nitro group. Meta substitution by these groups does not significantly attenuate dimerization (and explains what at first appears to be a discrepancy in the results obtained in [7] and [9], above). Surprisingly, substitution by -Cl also favors reduction to the aniline, to some degree, compared with unsubstituted nitrobenzene. Neither -CO$_2^-$ nor -SO$_3^-$ were effective in preventing dimerization.

The conversion of 3-nitro-4-hydroxybenzoic acid (1) to 2 is found to be facile in basic medium since it has the correct substitution pattern. This paper reports the scale-up of this process (Scheme 1) to yield > 35 kg of 2.

2. Experimental details

2.1. Cell design and synthetic procedures

The initial electrolysis vessel was an all-glass, beaker-type, two-compartment design of 15-ml capacity with a medium-porosity glass frit. The cathode compartment was kept under N$_2$ and contained a 4-cm^2 copper foil electrode. Oxygen evolved at the anode (4 cm^2 Pt) was vented. Magnetic stirring enhanced mass transport in both electrode compartments. Galvanostatic electrolysis at 7.5 mA cm^{-2} was performed at ambient (23° C) temperature. The cell voltage varied from 3.7 to 4.1 V over the course of the experiment for the electrolysis of a 0.5% w/v solution of 1 in 1 N NaOH.

An all-glass, flange-type cell similar to that described by Goodridge and King [11] was fabricated to allow examination of parameters in short electrolysis times. Mass transport was enhanced via nitrogen sparge through a glass frit on the bottom of the cell rather than by magnetic stirring. Convection by this means was adequate at current densities of ≤ 50 mA cm^{-2} for the concentrations of organics used this work (≥ 5% w/v).

A parallel-plate, filter-press assembly was used as a flow cell with a copper cathode and nickel anode separated by a cation exchange membrane. The membrane-to-electrode gap (1.5 mm) was defined by a viton rubber gasket which also dictated the 50-cm^2 electrode area. Polypropylene mesh between the membrane and electrode prevented contact. All-Teflon diaphragm pumps were used to provide flow rates of 300 ml min^{-1}. The anolyte and catholyte reservoirs were multineck glass round bottoms. Electrolysis of 25 g 1 in 250 ml 2 N NaOH was performed with 5 N NaOH as anolyte at 27–29° C until 120% of the theoretical charge was passed at 50 mA cm^{-2}. The

chromatographic yield and conversion were 98% (error estimated to be approximately ± 3%) and the current efficiency 82%. The cell voltage increased from 2.0 to 3.3 V during the synthesis and the catholyte volume increased linearly with charge due to the water of hydration of the charge carrier (Na$^+$). Chromatographic results were corrected for this increase.

Acidification of the catholyte with HCl, filtration of the amine-hydrochloride and subsequent hot filtration/recrystallization from 6 N HCl resulted in 19.2 g (68%) 2 (as the monohydrate hydrochloride salt) of > 99.9% purity.

Preliminary scale-up to convert a 10.4% w/v solution of 1 in 37 dm^3 of 2 M NaOH was accomplished in a cell similar to that described above at a larger scale. The parallel-plate flow cell contained nickel and copper electrodes (76 cm by 13 cm) separated by a cation exchange membrane. The anolyte was 5 N NaOH. Circulation was via centrifugal pumps and was 1.5 dm^3 min^{-1} and 0.6 dm^3 min^{-1} for the catholyte and anolyte, respectively. Controlled current electrolyses were performed on five batches (6–9 dm^3) of the aforementioned liquor at 100 A (101 mA cm^{-2}) initial current. The current was decreased stepwise to control the cell potential at 2.7 V giving an average current density of 78 mA cm^{-2}. Electrolysis was terminated when the conversion was ≥ 97% (the average charge was 110% of the theoretical six-electron process). The average yield (chromatographic) was 96% and the current efficiency was 88%. The isolated yield after work-up and recrystallization similar to that above was 90% of the monohydrate hydrochloride salt with an organic purity of ≥ 99.9%. A trickle current of 25 mA was used to keep the copper under negative polarization between runs to eliminate corrosion. It was necessary to keep the electrolytes under inert atmosphere between runs to prevent the formation of what was believed to be CuCO$_3$ on the copper surface, which can cause an ohmic resistance increase.

Scale-up to a facility capable of producing 22 kg of 2 per day was accomplished with a 0.56-m^2 monopolar cell stack consisting of 8 copper and 7 nickel electrodes with interspersed cation exchange membranes. Centrifugal pumps capable of 22 dm^3 min^{-1} were used. A 2000-A, 18 V rectifier was used and the 60-dm^3 polypropylene reservoirs were thermostatically controlled via stainless steel cooling coils immersed in the aqueous electrolytes. A trickle current of 0.25 A was used to maintain polarization in the cell between electrolyses and an atmosphere of N$_2$ was maintained over the electrolytes. Controlled-current electrolyses were performed batchwise on ten 36-dm^3 aliquots of 2 N NaOH containing an average of 21 mol 1. Initial currents of 1000 A were maintained until 70% of the theoretical charge was passed and then incrementally decreased to maintain the cell voltage below 3.0 V until the conversion was ≥ 97%. The average current density was 135 mA cm^{-2} and the current efficiency was 83% to result in a power consumption of < 2.6 kWh kg^{-1} (1.2 kWh lb^{-1}). Work-up similar to that above led to isolation of 36.6 kg of 99.9% pure 2.

2.2. Analytical

Liquid chromatography was utilized to monitor electrolyses with either a Varian 5000 and a Dupont 15 cm SCX column (15% $CH_3CN/0.02$ M KH_2PO_4, pH 2.85, $U = 2\,ml\,min^{-1}$) or with a Hewlett-Packard 1090 system and a 10-cm hypersil MOS column (75% $(2\,g\,dm^{-3}\,KH_2PO_4, 2\,g\,dm^{-3}$ sodium octane sulfonate), 25% ($2\,g\,dm^{-3}$ sodium octane sulfonate in MeOH), pH 2.5, $U = 0.5\,ml\,min^{-1}$). Authentic standards were used for calibration.

3. Results and discussion

3.1. Cyclic voltammetry

A copper electrode in aqueous NaOH (Fig. 1, voltammogram a) exhibits several surface waves which have been the subject of extensive investigations [12–15]. The processes associated with these surface waves will be briefly reviewed in order to facilitate an understanding of the catalytic effects.

A copper electrode poised at +0.400 V (vs NaCl-saturated calomel electrode (SSCE)) forms a relatively thick film of $Cu(OH)_2$ and/or CuO. During a negative-going scan, a relatively small wave at −0.63 V is observed which corresponds to a partial reduction of the copper(II) surface species to a duplex oxide consisting of Cu_2O and CuO. The wave at −0.991 V corresponds to reduction of the Cu_2O and CuO to copper metal.

Scan reversal at a potential of −1.2 V reveals an oxidation wave at −0.43 V that corresponds to formation of a film of Cu_2O that has barrier properties which limit its thickness. Continuing the scan to more positive potentials causes oxidation of this film and hence removal of the barrier allowing oxidation of the underlying surface to a much thicker film of $Cu(OH)_2$ and/or CuO (wave at −0.152 V).

Cyclic voltammetry of 1 at a copper electrode demonstrates the catalytic nature of the reduction (Fig. 1, voltammogram b). Upon addition of 0.515 M 1 to the electrolyte, the reductive surface wave at −0.991 V increases. (The reduction of 1 occurs at potentials 200–300 mV more negative than this at a glassy carbon electrode which is indicative of an over-

potential (kinetic limitation) at carbon or electrocatalytic activity at copper.) On the positive scan, the surface wave at −0.152 V is almost completely attenuated. These effects are interpreted as follows. Cu metal generated at −0.991 V chemically reduces 1 with formation of surface copper oxide and/or hydroxide. The surface oxidation wave at −0.152 V does not appear on the positive scan because the copper surface is already oxidized. Hence electrolysis of 1 at copper proceeds via chemical reduction with electrochemical regeneration of the copper surface; the reaction is electrocatalytic.

At lower concentrations of 1 (0.2 M), the surface oxidation wave was not attenuated at all. Apparently at the lower concentration, the regeneration of reduced copper surface was much faster than the reduction of 1, while at 0.515 M 1 the rates were comparable in the time frame (~ 1.2 s) of the scan at $100\,mV\,s^{-1}$.

3.2. Preparative electrolytic results

Electrolyses of 1 at relatively low concentrations (0.5% w/v) were first performed in a beaker-type cell with either 1 N NaOH or 0.1 N HCl (50% EtOH) as supporting electrolyte. In both cases, chemical yields (as determined by liquid chromatography (LC)) slightly above 90% with current efficiencies near 90% were obtained at 98% conversion. This indicates that N–N coupling was not a significant problem at low concentrations even in basic medium.

Several parameters were investigated during preliminary surveys. These were performed in an all-glass flange-type cell as described in the experimental section. The results indicated the following:

(a) Platinum, Ni, Pb, Sn, stainless steel, Co, Ag, carbon and Cu are all efficient electrodes for the conversion of 1 to 2 in a basic medium ($80\text{--}100\,mA\,cm^{-2}$) with chemical yields of 80–95% and current efficiencies in the same range at 6 F. However, Pb and Sn are corroded to a significant extent due to the electrocatalytic mechanism which appears to be somewhat faster at these electrodes than at Cu. (Cobalt was discolored which indicated a similar phenomenon at a somewhat lower rate.) The other aforementioned electrodes appeared to exhibit normal electron-transfer behavior.
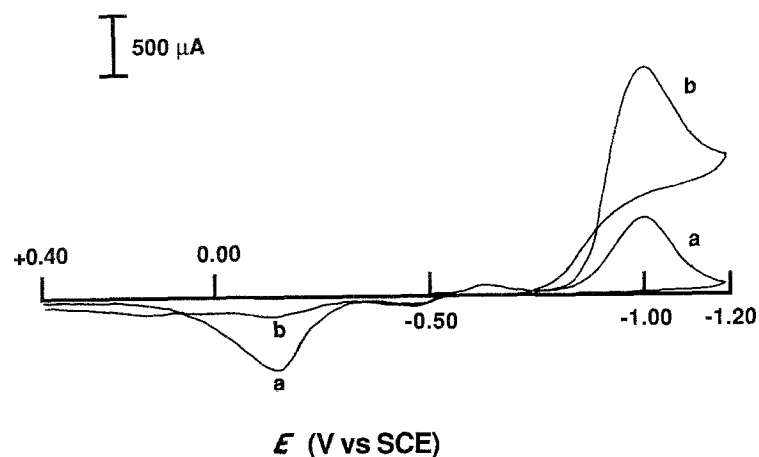

Fig. 1. Cyclic voltammetry at a copper electrode (geometric area 0.005 cm²) in 2 M NaOH + 0.5 M NaCl. Scan rate = 100 mV s⁻¹. Curve a: electrolyte only (no added organic). Curve b: electrolyte + 0.515 M 3-nitro-4-hydroxybenzoic acid (1).

Table 1. The effect of temperature, electrolyte, current density and membrane type on the conversion of 1 and the yield of 2.

Example	% Conversion	% Yield
Control[1]	83	85
5°C	78	72
60°C	91	86
1 M KOH	89	85
1 M K$_2$CO$_3$	88	82
1 M Na$_2$CO$_3$	80	75
1 M NaHCO$_3$	86	71
150 mA cm^{-2}	80	53
19 mA cm^{-2}	96	88
Anion exchange	85	53

[1] The control experiment was electrolysis of 1 (5% w/v) at a 6.3-cm^2 copper cathode in the flange-type cell with a cation-selective membrane at constant current (79 mA cm^{-2}) in 1 M NaOH (temperature controlled at 25°C) with nitrogen purge for mass transfer. The results were based on chromatographic analyses following passage of 6 F.

(b) At copper, only small temperature effects were noted (Table 1). Higher temperatures (e.g. 60° C) may be beneficial to minimize the solution resistivity. However, the chemistry cited by Treston [16] and Royals [17] must be taken into account at higher temperatures; certain substituted nitroaromatics (e.g. *o*-nitrobenzoic acid) encounter serious side reactions in base at elevated temperatures.

(c) Electrolyte cationic and anionic speciation are not critical (Table 1). For example, KOH, K$_2$CO$_3$, Na$_2$CO$_3$ and NaHCO$_3$ are all suitable electrolytes.

(d) Current densities from 20 to 150 mA cm^{-2} were examined in the flange-type cell. Even with the non-ideal mass transfer of the laboratory flange cell (insufficient agitation), only a small effect on current efficiency was noted at the higher current density. (For a discussion of mass transfer limitations see [18].)

(e) A cation-exchange membrane is preferable to an anion-exchange membrane because the organic anions (in basic solutions) can undergo active transport through the membrane via electromotive forces. Non-ionic separators can be used (e.g. the glass frit of the first example) although economic considerations on the amount of organic yield loss through the separators must be addressed.

For industrially significant concentrations of 1 (10% w/v) a 50-cm^2 flow cell (c) was used at the laboratory scale. Chromatographic results are shown in Fig. 2. Isolated yields of 72% (99.9% purity) were obtained after recrystallization. No evidence of N–N coupling was found .

Preliminary scale-up was accomplished in a filter-press cell similar to that described in (d) except with electrode dimensions of 0.1 m^2. Higher flow rates and better flow distribution result in an average current density of 78 mA cm^{-2} and isolated yields of 90% with 99.9% purity.

Scale-up to a facility capable of 22 kg day^{-1} (0.56 m^2) was accomplished and 10 batches containing a total of 211.5 mol 1 were converted cleanly to 2 at an average current density of 135 mA cm^{-2} at less than 3 V with current efficiencies > 80%. Isolation of
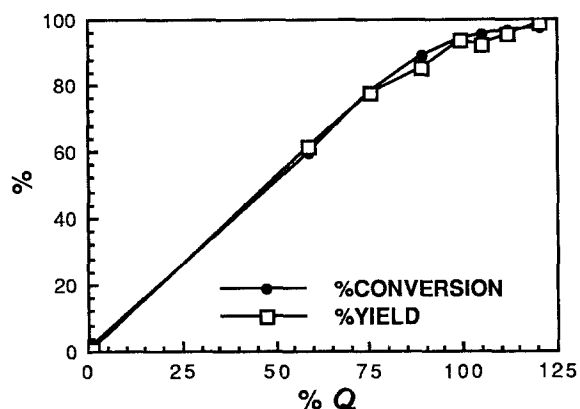

Fig. 2. Preparative electrolytic results for the reduction of a 10% w/v solution of 1 to 2 at a copper cathode in the 50-cm^2 parallel-plate flow cell displayed as % conversion and % yield as a function of the %Q (100 (coulombs/6 F mol)).

36.6 kg of polymer grade 2 (176 mol of the monohydrate hydrochloride) represents an 83% overall yield.

4. Conclusions

The high solubility of 1 in basic media and the ability to directly utilize a previous process stream without intermediate isolation make electrolysis in basic medium an attractive alternative to hydrogenation. With a monopolar cell excellent yields and current efficiencies were demonstrated for the synthesis of 2 (< 1.2 kWh lb^{-1}). This was a surprising result (this reduction requires 6 F) since less than 23% of all of the organic electrochemical processes which have reached the pilot stage had energy requirements this low [19]. Only six of these 17 piloted reactions were reductions.

The electrochemical synthesis of substituted anilines in basic media depends upon several factors, with the most important being the functionality and the positional isomerism of these substituents. We have demonstrated this chemistry on a large scale for one industrially important compound.

References

[1] R. H. McKee and C. J. Brockman, *Trans. Electrochem. Soc.* **62** (1932) 203.
[2] M. M. Baizer and H. Lund, 'Organic Electrochemistry', 2nd edn (1983) pp. 285–231.
[3] O. W. Brown and J. C. Warner, *Trans. Electrochem. Soc.* **41** (1922) 225.
[4] O. W. Brown and J. C. Warner, *J. Phys. Chem.* **27** (1923) 455.
[5] J. E. Weber and A. E. Meister, *J. Chem. Ed.* **27** (1950) 571.
[6] R. H. McKee and B. G. Gerapostolou, *Trans. Electrochem. Soc.* **68** (1935) 329.
[7] W. E. Bradt and E. J. Hart, *Trans. Electrochem. Soc.* **60** (1931) 205.
[8] G. Belot, S. Desjardins and J. Lessard, *Tet. Letters* **25** (1984) 5347.
[9] K. Honda, R. Yokouchi and S. Kikuchi, *J. Electrochem. Soc. Japan* **20** (1952) 15 (C.A. **46** 4930e).
[10] To be published.
[11] F. Goodridge and C. J. H. King, 'Technique of Electro-organic Synthesis Part 1' (edited by N. L. Weinberg), New York (1974) p. 81.
[12] N. A. Hampson, J. B. Lee and K. I. Macdonald, *J. Electroanal. Chem.* **32** (1971) 165.

[13]   S. M. Abd El Haleem and Badr G. Ateya, *J. Electroanal. Chem.* **117** (1981) 309.

[14]   L. M. Abrantes, L. M. Castillo, C. Norman and L. M. Peter, *J. Electroanal. Chem.* **163** (1984) 209.

[15]   R. L. Deutscher and R. Woods, *J. Appl. Electrochem.* **16** (1986) 413.

[16]   A. Treston, R. L. Blakeley and B. Zerner, *J.C.S. Chem. Comm.* (1980) 394.

[17]   E. Royals, 'Advanced Organic Chemistry', Prentice Hall (1954) p. 442.

[18]   N L. Weinberg and B. V. Tilak, 'Technique of Electro-organic Synthesis Part III', Wiley, New York (1982).

[19]   'A Survey of Organic Electrolytic Processes', Electrochemical Tech. Corp. ANL/OEPM-79-5, Argonne National Lab., for US Dept. of Energy under Contract W-31-109-Eng-38.