# Atypical Regioselectivity in the Electrochemical Reduction-Nucleophilic Substitution of 2-Nitroanisole

**Wendong Wang,[a] Guo-Zhang Wu,[a] and Peter G. Goekjian*[a]**

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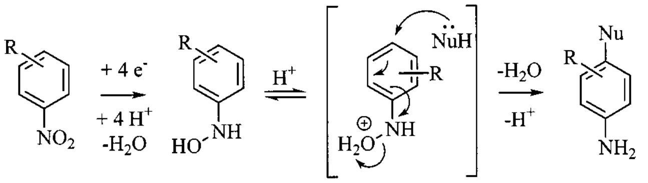
The electrochemical reduction-Bamberger substitution of 2-nitroanisole in 1 M $H_2SO_4$ yields predominantly 2,5-dimethoxyaniline, not the expected 2,4-isomer. The selectivity was found to be acid- and solvent-dependent, with lower acidity and less polar solvents favoring the formation of 2,4-dimethoxyaniline during galvanostatic electrolysis. A mechanistic working hypothesis involving an *ortho*-quinone monoimine dication is presented to direct further synthetic studies.

## Introduction

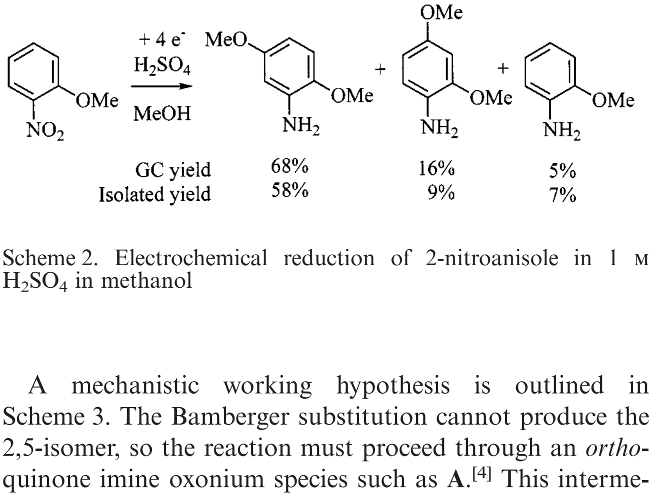
As part of a project on the electrochemical synthesis of natural products, we became interested in the electrochemical reduction-nucleophilic substitution of substituted nitrobenzenes.[1] The reaction proceeds through the electrochemical reduction of the nitro group to a hydroxylamine, followed by a Bamberger substitution (Scheme 1).[2] We were attracted by the fact that this reaction converts a nitrobenzene to an arylamine while simultaneously adding a nucleophile to the *para* position of the arene ring. The electrochemical reduction of 2-nitroanisole in 1 M $H_2SO_4$ in methanol, however, leads to atypical addition of the nucleophile to the *meta* position relative to the amine. The details are reported herein.



Scheme 1. Electrochemical reduction and nucleophilic substitution of substituted nitrobenzenes

## Results and Discussion

The electrochemical reduction of 2-nitroanisole in 1 M $H_2SO_4$ in methanol was expected to yield 2,4-dimethoxyaniline (2,4-DMA) as the major product in which the nucleophile is *para* to the amino group. Addition to the *ortho* position to yield 2,6-DMA was an expected side-reaction. In the event, we were surprised to find that *the reaction produces 2,5-DMA selectively*, with 2,4-DMA and anisidine as minor products (Scheme 2). To our knowledge, no examples of such regioselectivity have been reported in the reduction of 2-nitroanisole.[1,3] The atypical regioselectivity raises the possibility of obtaining either 1,2,4- or 1,2,5-trisubstituted aromatic compounds from a single, simple precursor. We therefore undertook a brief study to determine whether the selectivity could be modified, and if so, which factors influence the selectivity.



Scheme 2. Electrochemical reduction of 2-nitroanisole in 1 M $H_2SO_4$ in methanol

A mechanistic working hypothesis is outlined in Scheme 3. The Bamberger substitution cannot produce the 2,5-isomer, so the reaction must proceed through an *ortho*-quinone imine oxonium species such as **A**.[4] This intermediate is expected to be more electrophilic at the 4-position than at the 5-position, and it is therefore necessary to invoke a dication **B** as an intermediate. The reaction is run under strongly acidic conditions, the imine functionality is quite basic, and the rearrangement is believed to occur near the electrode surface.[5] The formation of a dication is therefore plausible. Alternatively, the formation of the ketal **C** by 1,2-addition to the oxonium could be followed by addition to the conjugated iminium functionality. The complexity of the reaction system makes rigorous mechanistic studies difficult,[6] and these hypotheses were therefore used only to guide experimental studies.

The mechanism via the dication **B** suggests that the regioselectivity may be acid- and solvent-dependent, with a weaker acid or a less polar solvent favoring the 2,4-isomer via the monocation **A**. In the event, decreasing the sulfuric acid concentration was found to reduce the selectivity, and the use of phosphoric acid or sodium hydrogen sulfate produced 2,4-DMA as the major product (Table 1).[7] The formation of anisidine and other side reactions become

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[a] Department of Chemistry, Mississippi State University
P. O. Box 9573, Mississippi State, MS 39762-9573, USA
Fax: (internat.) + 1-601/325-1618
E-mail: pgg1@ra.msstate.edu

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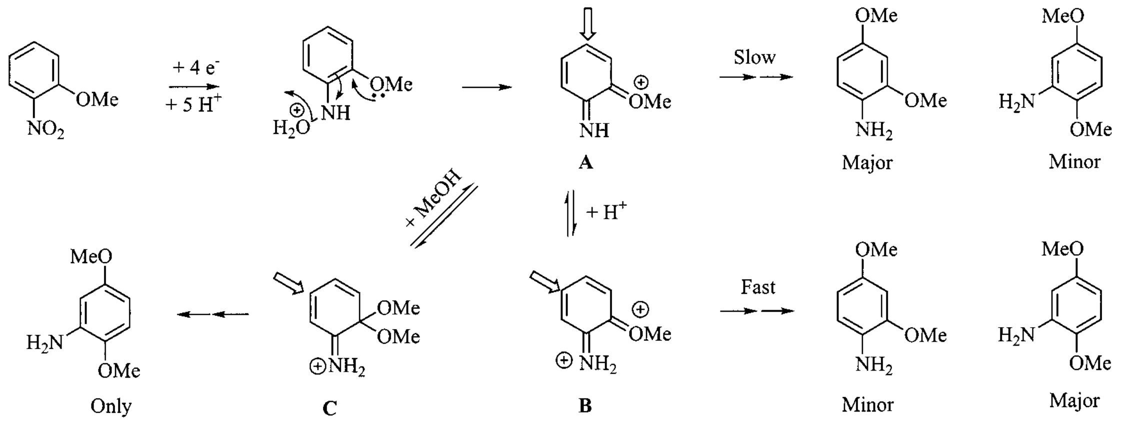


Scheme 3. Mechanistic rationale for the unexpected formation of 2,5-DMA in high yield.

Table 1. Effect of choice of acid on the regioselectivity (at >95% conversion)

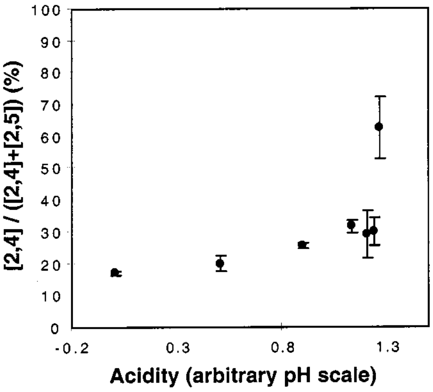
| Conditions | Solvent | 2,5-DMA | 2,4-DMA | Anisi-dine | Mass recov.[a] |
|---|---|---|---|---|---|
| 1.84 M $H_2SO_4$ | MeOH | 4.3 | 1 | 0.17 | |
| 0.92 M $H_2SO_4$ | MeOH | 4.2 | 1 | 0.17 | 87% |
| 0.46 M $H_2SO_4$ | MeOH | 2.6 | 1 | 0.25 | |
| 0.24 M $H_2SO_4$ | MeOH | 1.4 | 1 | 0.29 | |
| 0.11 M $H_2SO_4$ | MeOH | 1.4 | 1 | 0.58 | 55% |
| sat. $NaHSO_4$ 0.25 M $LiClO_4$ | MeOH | 0.43 | 1 | 1.74 | 44% |
| 15% $H_3PO_4$ 0.25 M $LiClO_4$ | MeOH | 0.25 | 1 | 0.35 | 37% |
| 10% $H_3PO_4$ 0.25 M $LiClO_4$ | MeOH | 0.06 | 1 | 0.29 | 23% |
| 5% $H_3PO_4$ 0.25 M $LiClO_4$ | MeOH | 0.0 | 1 | | 14% |

[a] 2,4-DMA + 2,5-DMA + anisidine.

competitive, and the yield drops sharply as the acidity is decreased. This is also consistent with the dication mechanistic hypothesis, as reducing the acid strength removes the fast pathway without accelerating the addition leading to the 2,4-isomer. The equilibrium between the monocation **A** and the ketal **C** is acid-independent, and this mechanism thus does not predict a substantial effect of the acid. Electrochemical parameters such as electrode material (Ni vs. Hg) or current/potential (5 to 20 mA/cm$^2$, –0.60 to –2.01 V) did not have a substantial influence on the selectivity. This is consistent with the regioselectivity-determining step being subsequent to the electrochemistry.

The experiments described above suggest an acid-dependence, but changing the ionic strength and concentration and nature of the acid may also influence the reaction, particularly in the electrochemical steps. In order to isolate the effect of the acid strength, a series of reactions were run in mixtures of sulfuric acid and tetrabutylammonium hydrogen sulfate ($TBAHSO_4$), keeping the total ion concentration constant. Although the tetrabutylammonium (TBA) ion and the proton cannot be considered rigorously equivalent, this was the best practical approximation. Lithium or sodium would have been preferable, but lack of solubility and the Lewis acidity of $Li^+$ precluded their use in this case. The reactions were run at 5 mA and ca. 15% conversion, and the product distribution was determined by GC.[8] The result is shown in Figure 1. The selectivity changes sharply as the acidity is decreased, in a manner consistent with an acid-dependent mechanism. The acidity near the electrode surface is difficult to determine accurately, and the effect of adsorbed water produced in the course of the reaction on the acidity further compounds the problem.[9] Therefore, the calculated aqueous pH was used as an arbitrary acidity scale.[10] An estimate of the acidity of the bulk solution using Malachite Green as an indicator gives an effective[11] pH of 1.3 (half-protonation of the indicator) for 0.1 M $H_2SO_4$/0.2 M $TBAHSO_4$ in anhydrous methanol (0.91 calculated pH). The corresponding experiments under constant potential rather than constant current gave more scattered results, presumably as a result of variations in the pH gradient at the electrode with changes in the current. In addition, the yield of DMAs drops to zero shortly above the pH at which the selectivity changes, suggesting either that the dehydration of the hydroxylamine becomes slow, or that side-reactions become overwhelming.

A large solvent effect was observed on the selectivity. The selectivity in 0.95 M $H_2SO_4$ decreased in going from methanol to 1:1 THF-methanol or 1:1 $CH_3CN$-methanol (Table 2). The effect was more pronounced in 0.1 M $H_2SO_4$/0.2 M $TBAHSO_4$, as the selectivity changed from 2.9:1 in favor of 2,5-DMA to 1:20 in favor of 2,4-DMA in 1:1 THF-methanol at 15% conversion. Water had a strong effect on



| $[H_2SO_4]$ | $[TBAHSO_4]$ | calc. pH |
|---|---|---|
| 1.0 M | - | (0.01) |
| 0.3 M | - | (0.51) |
| 0.1 M | 0.2 M | (0.90) |
| .032 M | .268 M | (1.13) |
| .013 M | .287 M | (1.21) |
| .005 M | .295 M | (1.24) |
| - | 0.3 M | (1.27) |

-$[TBAHSO_4]+[H_2SO_4] = 0.3M$
-Nitroanisole: 15 µL/36 mL
-7.5 coulombs, ca. 15% conversion;
-5 mA, constant current
-Hg electrode, divided cell
-Room temperature
-Ratios detd. by GC, 3 or 4 rxns
-Error bars: ±1 standard deviation

Figure 1. Regioselectivity vs. acidity (arbitrary scale) at 15% conversion and experimental conditions.

Table 2. Effect of solvent on regioselectivity (at 15% conversion)

| Conditions | Solvent | 2,5-DMA | 2,4-DMA |
|---|---|---|---|
| 0.95 M $H_2SO_4$ | MeOH | 4.8 | 1 |
| 0.95 M $H_2SO_4$ | 1:1 MeOH-$CH_3CN$ | 3.5 | 1 |
| 0.95 M $H_2SO_4$ | 1:1 MeOH-THF | 3.5 | 1 |
| 0.1 M $H_2SO_4$ + 0.2 M $TBAHSO_4$ | MeOH | 2.9 | 1 |
| 0.1 M $H_2SO_4$ + 0.2 M $TBAHSO_4$ | 1:1 MeOH-THF | 1 | 20 |
| 0.1 M $H_2SO_4$ + 0.2 M $TBAHSO_4$ | 0.02% $H_2O$ in 1:1 MeOH-THF | 1 | 1 |

the selectivity, as addition of 5 µL of water to 36 mL of methanol:THF (ca. 8 mM) was found to degrade the selectivity from 1:20 2,5-DMA: 2,4-DMA to a 1:1 mixture. This effect can be attributed to the unusual ability of water to stabilize polar intermediates relative to methanol:THF (Y-value $H_2O$: 3.493),[12] and possibly to adsorption of the water on the electrode surface. These results are consistent with the classical prediction that a polar solvent will have a stronger stabilizing effect on a dicationic transition state via **B** than on a monocationic transition state via **A**.

Preparative experiments were performed to confirm the GC results. In the strong acid case, the isolated yields are comparable to the GC yields, considering that the products are air-sensitive and somewhat volatile (Scheme 2). In the 2,4-DMA-selective mild acid case, the mass recoveries and yields are low (maximum yield of 2,4-DMA: 22%). This is not surprising in view of the narrow window of acidity which produces the desired selectivity, the competition from side-reactions, and the effect of the water produced during the reaction in degrading the selectivity. Diluting the reaction was found to improve the yield of 2,4-DMA substantially, suggesting that the major side reactions involve dimerization and/or polymerization. The yield of the anisidine by-product fluctuates widely. Addition of a radical scavenger (2,6-di-*tert*-butyl-4-methylphenol) had no significant effect. Although some effort was made to optimize the conditions, the rates of the side reactions depend on the structure of the specific product. Insofar as dimethoxyaniline is not our synthetic target, and is unusually electron-rich and hence prone to oxidation and polymerization, we feel that detailed optimization is best done on a more synthetically relevant system.

## Conclusions

The electrochemical reduction-nucleophilic substitution of 2-nitroanisole in 1 M $H_2SO_4$ in methanol gives primarily 2,5-DMA, not the expected 2,4- or 2,6-isomers. The selectivity can be altered by the choice of conditions, although the synthesis of the 2,4-isomer is not synthetically useful. The selectivity is controlled by the strength of the acid and the choice of solvent. Water produced during the reaction can have an effect on the selectivity. The dication working hypothesis will be used to direct synthetic studies. The scope of this reaction, including the addition of other nucleophiles and applications to natural product synthesis are being investigated.

## Experimental Section

**General:** 2-Nitroanisole, sulfuric acid, 2,4-DMA, 2,5-DMA, and $TBAHSO_4$ were purchased from commercial sources and used as received. Methanol was dried by distillation from $Mg(OMe)_2$, acetonitrile from $CaH_2$, and THF from benzophenone sodium ketyl. NMR spectra were obtained on a GE-omega 400 MHz or a QE-300 MHz NMR. GC's were measured on a Varian 3300 equipped with a DB-5 30m × 0.32 mm ID column using a 50:1 split ratio. Dodecane was used as an internal standard, and calibration curves were generated for 2-nitroanisole, 2,4-DMA, 2,5-DMA, and anisidine. Electrochemical experiments were performed using an EGG Princeton Applied Research Model 273A Potentiostat/ Galvanostat in either constant current or constant potential mode. Pt wire and Nickel wire gauze (40 mesh woven 0.13 mm Ni wire, STK# 39703) were purchased from Alfa-Aesar Scientific.

**Electrolysis of 2-Nitroanisole. – Strong Acid Conditions:** A solution of $H_2SO_4$ in methanol (0.92 M, 10 mL) was placed in the cathodic compartment of an electrolysis cell consisting of a 3-necked, 25 mL flask equipped with a working Hg pool electrode (surface area 1.8 cm$^2$), an Ag/AgCl reference electrode and an anodic compartment divided by a scintered glass disk, filled with the same solution and equipped with a Pt coil electrode. The solution was sparged with Argon for 10 min. 2-Nitroanisole (40 µL, 0.327 mmol) was added and cathodic electrolysis was carried out under constant current (10 mA/cm$^2$) to 171 C (1.36 times theoretical). The reaction mixture was transferred to a round-bottom flask, neutralized with 2.5 M KOH, and concentrated in vacuo to remove methanol. The resulting mixture was extracted with ethyl acetate and the organic layer was washed with distilled water (2 × 20 mL) and dried over sodium sulfate. The organic layer was filtered, diluted to 50.00 mL and analyzed by GC using 2,4-DMA and anisidine as external standards. The mixture was concentrated in vacuo and the purple residue was separated by silica gel chromatography in 4:1 $CHCl_3$:$CH_3CN$ to yield 2,5-DMA (28.0 mg, 0.183 mmol, 58% yield), 2,4-DMA (4.5 mg, 0.029 mmol, 9% yield), and anisidine (3 mg, 0.024 mmol, 7% yield). The identity of the products was established by comparison of the GC, TLC, and $^1H$ NMR in $CDCl_3$ to those of the authentic compounds.

**Mild Acid Conditions:** A solution of 2-nitroanisole (40 µL, 0.327 mmol), $TBAHSO_4$ (3.4 g, 0.28 M) and $LiClO_4$ (1.4 g, 0.37 M) in anhydrous methanol (36 mL) was electrolyzed according to procedure above, to yield 2,4-DMA (10.8 mg, 0.0704 mmol, 22%), 2,5-DMA (6.4 mg, 0.0417 mmol, 13%), anisidine (1.2 mg, 0.01 mmol, 3%), and an unidentified by-product (8 mg).

**Nickel Electrode:** Electrolysis was performed under the conditions above using a 2.75 cm$^2$ area Nickel flag-type electrode made from 40 mesh woven Nickel wire gauze. In all cases, results obtained with a Nickel electrode were comparable to those obtained with a mercury electrode.

**Other Acids:** A solution of the indicated acid ($H_2SO_4$, $H_3PO_4$, or $NaHSO_4$) and $LiClO_4$ (if applicable, 106 mg, 1.0 mmol) in anhydrous methanol (10 mL solution) was electrolyzed according to procedure above. Under preparative constant current conditions, the electrolysis was continued to 1.3–1.5 times theoretical charge. Under constant potential conditions, a cyclic voltammetry scan was performed and the potential was selected accordingly (typically in the middle of the rise for reproducibility; no effect of the potential (–0.6 V to –0.85 V) was observed on the product distribution in parallel experiments).

**Effect of Acid Strength:** A solution of $Bu_4NHSO_4$ and sulfuric acid in the indicated ratio (0.3 M combined) in dry methanol (36 mL) in the apparatus described above was sparged with argon presaturated with methanol for 10–15 min. 2-Nitroanisole (15 µL, 0.12 mmol) was added and the mixture was electrolyzed at constant current (5 mA) to 7.5 C (15% of theoretical). The reaction was worked up as above, and analyzed by GC using a dodecane internal standard.

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[5] The postulate that the rearrangement occurs near the electrode surface has been invoked by Lund to explain the observation that the Bamberger rearrangement occurs substantially faster during the electrochemical reduction than it does with the isolated hydroxylamine. (ref.[1]) This postulate can similarly help justify a dication intermediate. Induced polarization of the solvent near the electrode surface may stabilize the highly charged species. E. M. Kosower, *An Introduction to Physical Chemistry*, Wiley Sons, New York, **1968**; Part 2.

[6] A more rigorous study could be performed on isolated hydroxylaminoanisole, but the electrode surface plays a role in the Bamberger rearrangement in this case (refs.[1,5]). Therefore, the results from such a study, although potentially very interesting, would not be applicable to the electrochemical version of the reaction.

[7] A similar dependence of the selectivity on the acid concentration has been observed in the Pt-calyzed hydrogenolysis of 2-nitroanisole. However, the major product was assigned as 2,6-dimethoxyaniline rather than 2,5-dimethoxyaniline. T. Sone, Karikura, M. S. Shinkai, O. Manabe, *Nipp. Kagaku Kaishi* **1979**, 1532.

[8] Yields could not be determined accurately at low conversion.

[9] C. H. Rochester, *Acidity Functions*, Academic Press, London, **1970**; p 217–223. A. S. Kislina, M. Y. Kulikova, S. G. Sysoeva, O. N. Temkin, *Russ. Chem. Bull.* **1994**, *43*, 1626.

[10] Using a p*K*a of –3 for $H_2SO_4$ and a p*K*a of 1.92 for $HSO_4^-$.

[11] The terms acidity and effective pH are used in this paper as measures of the ability of the solution to protonate a weak base, as opposed to a measure of the proton concentration. Malachite green, p*K*a 1.3 in water, is a cationic amine and its protonation is a reasonable model for the **A** to **B** equilibrium.

[12] The *Y*-value relates the rate of solvolysis of *tert*-butyl chloride in a given solvent to the rate in 20% water: 80% ethanol; $Y = \log k$ (solvent) – $\log k$ (80:20 EtOH:$H_2O$). Methanol, $Y = –1.080$; 10% water: 90% dioxane = –2.030. A. H. Fainberg, S. Winstein, *J. Am. Chem. Soc.* **1956**, *78*, 2770 and refs. cited therein. See also ref.[5]

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