Electrochemical Amination. Selective Introduction of Two Amino Groups into an Aromatic Ring

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Abstract—Indirect cathodic amination of anisole via a Ti(IV)–NH₂OH system in aqueous solutions of sulfuric acid is studied. The major products of the radical cation substitution in these media are *para-* and *ortho-*anisidines and 4-methoxy-1,3-phenylenediamine. The most efficient electrochemical process takes place in 10–12 M H_2SO_4 . Under these conditions, complete conversion of the source of amino radicals is observed, and the total current yields, which correspond to the yields per hydroxylamine, reach 60%.

Keywords: cathode, Ti(IV)/Ti(III) mediator system, hydroxylamine, anisole, radical cation aromatic substitution, 4-methoxy-1,3-phenylenediamine

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The chemical amination of aromatic substrates with hydroxylamine and transition metal compounds in acidic aqueous and aqueous-organic media most commonly form isomeric monoamino derivatives as major products [1–9]. Electrochemical functionalization in dilute sulfuric acid solutions gives the same results [10–13]. However, in catholytes with H₂SO₄ concentrations higher than 7 M, a deeper substitution takes place, specifically, diamino derivatives are formed in significant amounts along with monosubstitution products [12, 13].

Until now consecutive introduction of two amino groups to the aromatic ring has been studied with only one substrate, namely benzene [12, 13]. The goal of the present work was to find out how the acidity of the sulfuric acid electrolyte affects the results of amination of anisole, a compound containing a substituent that makes the aromatic ring more reactive toward amino radical cations.

The electrolysis of the Ti(IV)–NH₂OH–C₆H₅OMe system was performed in 1.5–15 M aqueous H₂SO₄ under conditions favoring the synthesis of isomeric anisidines in aqueous-organic electrolytes containing sulfuric acid [14, 15]. Anisole was taken in a large excess with respect to hydroxylamine (0.046 and 0.005 mol, respectively), and, therefore, as the main

substitution efficiency criterion we used the total current yield of amino compounds. Unlike the conditions used in [12, 13] for benzene amination, the quantity of electricity passed through the catholyte (482.4 C) was enough for not only partial, but also for complete theoretical conversion of hydroxylamine, based on the consumption of one electron per hydroxyl-amine molecule. To prevent electrochemical release of hydrogen in 1.5-10 M H₂SO₄ solutions we used a mercury cathode, and, in more acidic media, when mercury can be oxidized by Ti(IV), a platinum electron was used.

The amination of anisole in 1.5 M H₂SO₄ gives not only isomeric anisidines, but also 4-methoxy-1,3phenylenediamine 1. The current yields of anisidines and diamine 1 at 20°C are 5.9 and 1.6%, respectively (Fig. 1a). As the H₂SO₄ concentration is increased up to 4.5 M, the total substitution efficiency decreases (Fig. 1b). The decrease of the amination yield is associated with fact that reaction (1) involves exclusively the unprotonated form of hydroxylamine [12, 13], and the concentration of this form decreases upon the increase of the acidity of the electrolyte. Increasing concentration of Ti(III) generated both on the cathode and by methoxyaminocyclohexadienyl radical cations with Ti(IV) increases the fraction of



Fig. 1. (a) Effect of H₂SO₄ concentration on the (*1*, *1*') current yield of methoxyphenylynydiamine 1 and (*2*, *2*') total yield of isomeric anisidines and (b) (*3*, *3*') total current yield of all indirect anisole amination products on a (*1*–3) mercury cathode (11.0 cm²) at 20°C and (*1*–3') platinum cathode (8.2 cm²) at 40°C. (×) Data obtained in 4.5 and 10 M H₂SO₄ on a Hg cathode at 40°C and on a Pt cathode at 20°C, respectively ([Ti(IV)] = 0.1 M, [NH₂OH] = 0.2 M, *i* = –2 mA/cm²).

[H₂SO₄], M

aminyl radicals consumed in reaction (2) that competes with substitution.

$$\mathrm{Ti}(\mathrm{III}) + \mathrm{NH}_{2}\mathrm{OH} \rightarrow [\mathrm{Ti}(\mathrm{IV})\mathrm{NH}_{2}]^{-} + \mathrm{OH}^{-}, \qquad (1)$$

$$[\text{Ti}(\text{IV})\text{NH}_2] + \text{Ti}(\text{III}) \xrightarrow{H} 2\text{Ti}(\text{IV}) + \text{NH}_3.$$
(2)

The slight increase in the current yield of diamine 1 and even stronger decrease in the total yield of anisidines under these conditions (Fig. 1a) point to the fact that a certain fractionof anisidinium ions are activated as the acid concentration increases.

The isomer distribution of phenylenediamines observed during the electrochemical amination of benzene and aniline [12, 13], as well as the ion molecular composition of aqueous solutions of H₂SO₄, reported in [16], suggest that aniline and its monosubstituted derivatives in sulfuric acid media can exist as ArNH₃⁺ cations, ArNH₃⁺, HSO₄⁻ ion pairs, and ArNH₂, HSO₄ associates formed by the reaction of aminium and sulfate ions. Compound 1 is the only anisole diamination product. Consequently, taking into account the isomer com-position of anisidines (Fig. 2), we can suppose that the increase of its current yield (Fig. 1a) is associated with increasing concentrations of p-MeOC₆H₄NH₃⁺, HSO₄⁻ and o-MeOC₆H₄NH₃⁺, HSO₄ ion pairs in the catholyte. The charge of the ammonium ion in the ion pairs is compensated by the charge of the counterion (the effect of the positive charge on the aromatic ring is exclusively through the field effect), and, therefore, the reactivity of the

aromatic ring toward amino radical cations and the substitution regioselectivity are mainly associated with the presence of the methoxy group.

In the catholytes containing H_2SO_4 concentra-tions higher than 5 M, because of the increased solubility of anisole, increased concentration of ion pairs, and decreased rate of reaction (2) explained by the shift of equilibrium (3) to the right, an increase of the total yield of mono- and diamino derivatives is observed (Fig. 1b). Therewith, the current yield of methoxyphenylenediamine increases to the greatest extent (Fig. 1a). The only product whose yield in these media further decreases is *meta*-anisidine (Fig. 2).

$$[\operatorname{Ti}(\mathrm{IV})\mathrm{NH}_2]^{\cdot} + \mathrm{H}^+ \rightleftharpoons \operatorname{Ti}(\mathrm{IV}) + \mathrm{NH}_3^{+\cdot}.$$
(3)

The total efficiency of the indirect amination of anisole in 10 M H_2SO_4 on a mercury electrode is as high as 59.9% (Fig. 1b). The replacement of the mercury electrode by a platinum electrode does not increase the yield of amino compounds under these conditions, though the smaller area of the latter electrode leads to a lower rate of reaction (2) because of the lower intensity of the cathodic generation of Ti(III). This result is likely to be associated with the electro-chemical release of hydrogen (Fig. 3), which becomes appreciable, when the potential of the platinum electrode is below -0.18 to -0.20 V.

Raising the experimental temperature to 40°C eliminates the problems associated with the use of a

 $[H_2SO_4], M$



Fig. 2. Dependence of the current yield of (1, 1') meta-, (2, 2') para-, and (3, 3') ortho-anisidines on H₂SO₄ concentration during the indirect anisole amination on a (1-3) mercury cathode at 20°C and (1'-3') platinum cathode at 40°C. (×) Data obtained in 4.5 and 10 M H₂SO₄ on a Hg cathode at 40°C and on a Pt cathode at 20°C, respectively.

platinum cathode (Fig. 3) and makes it possible to aminate anisole not only in 10 M H_2SO_4 , but also in less acidic solutions, in particular, in 8 M H_2SO_4 (Figs. 1 and 3). The nature of the cathode material has almost no effect on the composition of the aromatic amination products, because the role of the electrode in the electrochemical process is to reduce Ti(IV) exclusively [12, 13].



Fig. 3. Change in the potential of the (1-3) platinum and (4) mercury cathode at (1, 4) at 20°C and (2, 3) 40°C in aqueous solutions of (2) 8, (1, 4) 10, and (3) 15 M H₂SO₄.

The amination efficiency remains almost invariable in 10–12 M acid solutions and then sharply decreases (Fig. 1b). The dependences of the current yield of phenylenediamine **1** and the total current yield of anisidines on H₂SO₄ concentration peak at 10 and 13.5 M acid concentrations (Fig. 1a) respectively. The decrease of the current yield of diamine **1** is accompanied by the sharpening of the slope of the dependence of the total current yield of anisidines (Fig. 1a). This points to a decrease in the rate of the reaction of monoamines with amino radical cations in media with a high protogenic activity, and, apparently, to a decrease in the concentration of the *p*-MeOC₆H₄NH₃⁺, HSO₄⁻ and *o*-MeOC₆H₄NH₃⁺, HSO₄⁻ ion pairs.

4-Methoxy-1,2-phenylenediamine **2** along with diamine **1** are produced in the catholytes containing 9–14 M H_2SO_4 . The highest current yields of about 0.2% for compound **2** were observed in 11–13 M solutions. Such a low yield of the product suggests that these media contain very little of the associate of *para*-anisidine molecule and hydrosulfate ion. The low concentration of the associate is obviously explained the electron-donor effect of the methoxy group, which enhances the strength of bonds in the ⁺NH₃ group. As a result, anisidines, unlike aniline [12, 13], are present in sulfuric acid media almost exclusively as anisidium cations, both free and ion-paired.



Fig. 4. Distribution of (1) para-, (2) ortho-, and (3) metaanisidines in H_2SO_4 solutions at 40°C.

The decrease in the total yield of isomeric anisidines at H₂SO₄ concentrations higher than 13.5 M (Fig. 1a) is associated with the protonation and sulfonation of anisole, as well as by the formation of diprotonated anisidines (anisidine dications, similarly to isomeric phenylenediamine dications [12, 13], do not react with the electrophilic radical cations ⁺NH₃). The protonation of the anisole methoxy group is evidenced by an increase in the current yield of meta-anisidine in 10-13.5 M H₂SO₄ solutions (Fig. 2) and a sharp decrease of the fraction of ortho-anisidine among the resulting anisidines in solutions with H₂SO₄ concentrations higher than 13 M (Fig. 4). The sulfonation of the aromatic substrate is evidenced by the lower currents vield of all the three isomeric anisidines at acid concentrations higher than 13.5 M (Fig. 2) and the dependence of the mass of anisole remaining after electrolysis on H₂SO₄ concentration (Fig. 5). At 40°C appreciable anisole sulfonation begins to occur at H_2SO_4 concentrations higher than 11–12 M (Fig. 5). Note that since the aromatic substrate was taken in a large excess with respect to the source of amino radicals, we did not give considerable attention to the completeness of the substrate transfer from the electrochemical cell to the extract; the cell was only five times washed with water. Inspite of this the efficiency of the transfer was quite high. For example, formation the obtained amounts of anisidines and



Fig. 5. Effect of H_2SO_4 concentration on the weight of anisole remaining after the electrolysis of the Ti(IV)–NH₂OH–C₆H₅OMe system on a (1) mercury cathode at 20°C and (2) platinum cathode at 40°C. (×) Data obtained in 4.5 and 10 M H₂SO₄ on a Hg cathode at 40°C and on a Pt cathode at 20°C, respectively.

methoxyphenylenediamines in 10 M H_2SO_4 requires about 0.19 g of anisole, which fairly agrees with the data in Fig. 5.

After completion of amination in 8–13 M acid, the catholytes had colors characteristic of Ti(III) solutions, from light to black violet. The catholytes containing 13.5–15 M H₂SO₄ were dark cherry-colored and changed color to violet on dilution with water. Adding hydroxyl-amine sulfate to dilute catholyte samples led to a disappearance of the violet color. This fact suggests that hydroxylamine is completely consumed on electrolysis in 8–15 M H₂SO₄ solutions and that the current yields of anisole amination products correspond to the yields for the amino radical source.

At the end of this research, to assess the relative contribution of *para-* and *ortho-*anisidines to phenylenediamine 1 formation, we performed amination of these substrates in 10 M H₂SO₄ at 40°C. The electrolysis of the Ti(IV)–NH₂OH–*p*-MeOC₆H₄NH₂ gave diamines 1 and 2 with the yields of 64.3 and 0.46% per current and hydroxylamine respectively. The amination of *ortho-*anisidine resulted in formation of compound 1 exclusively (current yield 58.8%). The yields of diamino compounds per anisidine in both cases were quantitative. These results, as well as the data in Fig. 2, allow us to state that *para-*anisidine contributes more to the formation of phenylenediamine 1 that the *ortho* isomer. Thus, we presented here a fairly rare precedent of a highly selective radical cation process, where the consecutive introduction of two groups into an aromatic ring leads to an almost exclusive formation of one disubstitution product, namely 4-methoxy-1,3-phenylenediamine.

EXPERIMENTAL

The amination of anisol and *para-* and *ortho*anisidines was performed in a three-electrode glass electrochemical cell equipped with a reflux condenser, a thermostatic jacket, and a ceramic diaphragm between the cathode and anode compartments. The design of this cell allows use of both a platinum (8.2 cm²) and a mercury (11.0 cm²) cathodes with the constant surface area of the latter under vigorous stirring of the catholyte.

The catholyte (25 mL) contained sulfuric acid of required concentration, 0.1 M Ti(IV), and 0.2 M NH₂OH. The highly dispersed emulsion of 5 mL of the aromatic substrate in the electrolyte was obtained by means of magnetic stirring. Before electrolysis the oxygen dissolved in the emulsion was removed by bubbling argon passed through a Drexel bottle filled with an aqueous solution of H₂SO₄ and C₆H₅OCH₃. As the inert gas was bubbled through the catholytes with 14 and 15 M H₂SO₄, the anisole phase disappeared. In the course of electrolysis argon was passed over the emulsion or solution (in 13.5 M H₂SO₄ the two-phase system transformed into one-phase).

The concentrations of anisidines in $10 \text{ M H}_2\text{SO}_4$ were 0.2 M, the cathode was a platinum electrode.

The amination of the aromatic substrates was performed using Autolab PGSTAT 302N or IPC-Pro MF potentiostats galvanostats at a current density of -2 mA/cm^2 . The computer control of cathode current and potential (measured against a silver chloride electrode) was duplicated by means of GDM 8145 and Keithley 2000/E multimeters, respectively. For reproducible potentials, before electrolysis the platinum electrode was washed with acetone and water and then subjected to anodic–cathodic polarization in aqueous sulfuric acid of required concentration at a current density of ± 0.5 A. The anode was a platinized platinum, and the anolyte was aqueous H₂SO₄ with the same concentration as in the catholyte.

After electrolysis the emulsion $(1.5-13 \text{ M H}_2\text{SO}_4)$ or solution $(13.5-15 \text{ M H}_2\text{SO}_4)$ of anisole in the electrolyte, as well as solutions of anisidines in 10 M H₂SO₄ were allowed to stand at the experimental temperature for an additional 10 min. The catholyte was then diluted with cold water to obtain the final H_2SO_4 concentration of about 1.5 M, then rendered weakly acidic by adding saturated aqueous NaOH under cooling, and finally neutralized with NaHCO₃. The electrolysis products were extracted with chloroform.

Analysis of the resulting amines was performed on a Khromatek Kristall 5000.2 with flame ionization detector, the temperature of a CP-Sil 8 CB capillary column (60 m \times 0.25 mm \times 0.25 µm) and the helium pressure were 160°C and 200 kPa, respectively. The qualitative composition of the amination products was also determined on a Chrom-5 chromatograph (flame ionization detector, glass columns 3.5 m \times 3 mm, liquid phases XE-60 and SE-30).

The following chemicals were used: 15% solution of titanium(IV) sulfate in aqueous 4 M H₂SO₄ (analytical grade), H₂SO₄ (chemical grade), hydroxylamine sulfate (Acros, 99%) recrystallized from water, NaOH (analytical grade), NaHCO₃ (chemical grade), distilled anisole (Acros, 99%), chloroform (analytical grade), ortho- and meta-anisidines (Lancaster, 98 and 99%) distilled in a vacuum over KOH (Acros, 85%), sublimed para-anisidine (Lancaster, 99%), as well as 4-methoxy-1,3-phylenediamine and 4-methoxy-1,2phylenediamine prepared by neutralization of their sulfate (Aldrich, 98%) and hydrochloride (Lancaster, 98%), commercial mercury (P0) purified by simultaneous treatment with air oxygen and 10% aqueous solution of distilled HNO₃ (chemical grade), and twice distilled water.

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REFERENCES

- 1. Davis, P., Evans, M.G., and Higginson, W.C.E., J. Chem. Soc., 1951, no. 10, p. 2563.
- Seaman, H., Taylor, P.J., and Waters, W.A., J. Chem. Soc., 1954, no. 12, p. 4690.
- Albisetti, C.J., Coffman, D.D., Hoover, F.W., Jenner, E.L., and Mochel, W.E., *J. Am. Chem. Soc.*, 1959, vol. 81, no. 6, p. 1489.
- 4. Minisci, F., Synthesis, 1973, no. 1, p. 1.
- Citterio, A., Gentile, A., Minisci, F., Navarrini, V., Sarravalle, M., and Ventura, S., *J. Org. Chem.*, 1984, vol. 49, no. 23, p. 4479. doi 10.1021/jo00197a030
- 6. Kuznetsova, N.I., Kuznetsova, L.I., Detusheva, L.G.,

Likholobov, V.A., Pez, G.P., and Cheng, H., J. Mol. Catal. A, 2000, vol. 161, nos. 1–2, p. 1. doi 10.1016/S1381-1169(00)00206-5

- Zhu, L.F., Guo, B., Tang, D.Y., Hu, X.K., Li, G.Y., and Hu, C.W., J. Catal., 2007, vol. 245, no. 2, p. 446. doi 10.1016/j.jcat.2006.11.007
- Parida, K.M., Dash, S.S., and Singha, S., *Appl. Catal. A: General*, 2008, vol. 351, no. 1, p. 59. doi 10.1016/ j.apcata.2008.08.027
- Parida, K.M., Rath, D., and Dash, S., J. Mol. Catal. A, 2010, vol. 318, nos. 1–2, p. 85. doi 10.1016/ j.molcata.2009.11.011
- 10. Tomat, R. and Rigo, A., J. Electroanal. Chem., 1977, vol. 75, p. 629.
- 11. Steckhan, E., Anwendung indirekter Elektrolysen fur organische Synthesen und Spektroelektrochemische

Untersuchung anodischer Olefinoxidationen: Habilitationsschrift, Münster: Westfalischen Univ., 1977.

- Lisitsyn, Yu.A. and Kargin, Yu.M., Russ. J. Electrochem., 2000, vol. 36, no. 2, p. 89. doi 10.1007/ BF02756893
- 13. Lisitsyn, Yu.A., Kargin, Yu.M., and Busygina, N.V., *Ross. Khim. Zh.*, 2005, vol. 49, no. 5, p. 121.
- Lisitsyn, Yu.A. and Sukhov, A.V., Russ. J. Electrochem., 2011, vol. 47, no. 10, p. 1180. doi 10.1134/ S1023193511100120
- Lisitsyn, Yu.A. and Sukhov, A.V., Russ. J. Electrochem., 2013, vol. 49, no. 1, p. 91. doi 0.1134/ S1023193513010126
- 16. Librovich, N.B. and Maiorov, V.D., *Izv. Akad. Nauk* SSSR, Ser. Khim., 1977, no. 3, p. 684.