

## Studies on Electrolytic Substitution Reactions. IX.\* Anodic Cyanation of Aromatic Ethers and Amines in Emulsions with the Aid of Phase Transfer Agents

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The anodic cyanation of di- and trimethoxybenzenes and *N,N*-dimethylbenzylamine has been studied in an emulsified system of methylene chloride, tetrabutylammonium sulfate, substrate, and aqueous sodium cyanide. The emulsification technique proved useful from the points of view of easy work-up and low applied voltage as compared to the corresponding homogeneous systems. The use of methylene chloride as the organic solvent component results in a less selective process than in acetonitrile/tetraalkylammonium salt, as evidenced by the fact that both methoxyl and hydrogen substitution take place, that dicyanation products are formed, and that *N,N*-dimethylbenzylamine is substituted in both the methyl and methylene group in the former solvent.

The anodic cyanation of organic compounds takes place by substitution of a ring hydrogen<sup>1-6,8,9,12,13</sup> or methoxyl group<sup>8</sup> in an aromatic compound, by substitution of a hydrogen  $\alpha$  to the nitrogen atom of a tertiary amine,<sup>8</sup> or by addition across a system of double bonds in a few cases.<sup>7,11</sup> Mechanistically, the reaction is of the direct type, most likely proceeding *via* an ECE mechanism.<sup>14,15</sup>

In practice, the reaction is performed either in methanol/sodium cyanide<sup>1-7,9,11-13</sup> or acetonitrile/tetraethylammonium cyanide<sup>8,9,10</sup> at a platinum anode, generally with low yields of cyanation products except for a few cases of rather special substrates, such as methoxybenzenes,<sup>8</sup> diphenylacetylene,<sup>9</sup> 9,10-dialkylanthracenes,<sup>10</sup> and uracil.<sup>11</sup> The most often encountered

side-reaction is anodic methoxylation when the reaction is performed in methanolic medium.

We have recently shown<sup>16</sup> that the use of an emulsified aqueous-organic system, consisting of aqueous sodium cyanide/methylene chloride-substrate-phase transfer reagent (such as tetrabutylammonium ion, added in the form of the sulfate), results in a clean, high-yield cyanation process. The reaction was exemplified by the monocyanation of naphthalene and anisole in maximally 69 and 57 % isolated yields, respectively, on the 0.05 mol scale. The phase transfer reagent is added in essentially catalytic amounts and serves for the transport of cyanide ion from the aqueous to the organic phase.<sup>17</sup> As an additional bonus, the aqueous phase acts as a high-conductivity medium for the transport of charge, as shown by the 5–15 fold decrease in cell voltage as compared to an entirely non-aqueous system of the same composition as the organic phase of the two-phase system.

Since this technique appears to hold promise for synthetic applications of organic electrochemistry,<sup>16</sup> we have now extended these studies to the cyanation of a number of other substrates, mainly di- and trimethoxybenzenes, as outlined in the following report.

### RESULTS AND DISCUSSION

*Electrolysis procedure.* Generally, electrolyses were performed in a jacketed vessel between a platinum foil anode (in a few experiments, it was established that graphite electrodes do give

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Table 1. Anodic cyanation of dimethoxybenzenes. Electrolyte: Aqueous 1 M NaCN (100 ml), methylene chloride (100 ml), Bu<sub>4</sub>NSO<sub>4</sub>H (10 mmol), substrate (10 mmol).

Dimethoxy- benzene	Products	Yield, <sup>a</sup> %	
		Emulsion system <sup>b</sup>	CH <sub>3</sub> CN/ Et <sub>4</sub> NCN <sup>c</sup>
1,2-	2-Methoxybenzotrile	26	94
	3,4-Dimethoxybenzotrile	11	
	Other products <sup>d</sup>	< 5	
1,3-	2,4-Dimethoxybenzotrile	58 <sup>e</sup>	12
	4,6-Dimethoxyisophthalonitrile	2 <sup>e</sup>	
1,4-	4-Methoxybenzotrile	40	90 – 95
	2,5-Dimethoxybenzotrile	3	
	Other products <sup>f</sup>	< 5	

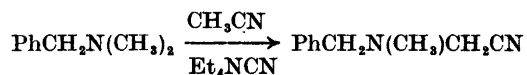
<sup>a</sup> Analyzed by GLC and based on unrecovered starting material. <sup>b</sup> This work; 3 F/mol of substrate passed. <sup>c</sup> Ref. 8. <sup>d</sup> According to mass spectral analysis, these products are probably 2,3-dimethoxybenzotrile, an isomer of dimethoxydicyanocyclohexadiene, and an isomer of dicyanoanisole. <sup>e</sup> In an experiment in which 6 F/mol of substrate were passed, 33 and 12 % of mono- and dicyanation product, respectively, were obtained. <sup>f</sup> According to mass spectral analysis, these products are probably two isomers of dimethoxydicyanocyclohexadiene.

similar results, albeit with much lower current efficiency) and a stainless steel cathode. This cathode material is advantageous because it does not support the cathodic reduction of methylene chloride to chloride ion, a troublesome side-reaction in an undivided cell<sup>18–20</sup> due to subsequent chlorine formation at the anode. Unless otherwise noted, the aqueous phase was 1 M in sodium cyanide and emulsified with an equal volume of the organic phase, a solution of the substrate in methylene chloride. The phase transfer agent, tetrabutylammonium hydrogen sulfate, was first neutralized and then added in an amount so as to make the whole system 0.05 M. Emulsification was achieved by a special high-speed stirrer, constructed in our Laboratory after the principles used for the commercially available "Ultra-Turrax" stirrer.<sup>21</sup> Constant current conditions were used throughout.

**Dimethoxybenzenes.** Table 1 shows products and yields from the emulsion electrolysis of the three dimethoxybenzenes, as well as those obtained in the homogeneous system, acetonitrile/tetraethylammonium cyanide.<sup>8</sup> Generally, the results indicate a more selective cyanation process in the latter electrolyte system, as evidenced by the almost quantitative yield of products derived by methoxyl substitution from 1,2- and 1,4-dimethoxybenzene. In the emulsion

system, both substitution of methoxyl and hydrogen takes place, and besides, dicyanation occurs to some extent.

The lower selectivity of the emulsion system is most likely a reflection of the properties of methylene chloride/tetrabutylammonium cyanide as a supporting electrolyte and not of the emulsion system in itself. We investigated this problem somewhat more in detail by electrolyzing *N,N*-dimethylbenzylamine in methylene chloride/tetrabutylammonium cyanide (0.1 M). This reaction was deemed very well suited for this purpose, since Andreades and Zahnov<sup>8</sup> had found that cyanation in acetonitrile/tetraethylammonium cyanide takes place exclusively in the methyl group:



This result is the more surprising considering the fact that anodic methoxylation takes place both in the methylene and methyl groups of this substrates.<sup>22–25</sup> We checked these results in acetonitrile, using tetrabutylammonium instead of tetraethylammonium cyanide, and obtained exclusive methyl substitution product, exactly as found by Andreades and Zahnov.<sup>8</sup> However, in methylene chloride/tetrabutylammonium cyanide the selectivity for methyl group substi-

Table 2. Anodic cyanation of 1,3-dimethoxybenzene, using different ratios between the two phases. Aqueous phase, 1 M NaCN; organic phase, methylene chloride; total volume, 200 ml; amount of substrate, 10 mmol.

Volume ratio aqueous/organic phase	Tetrabutylammonium ion, mmol	Charge passed, F/mol	Yield <sup>a</sup> of 2,4-dimethoxybenzonitrile, %	Current yield
1.0	10	3	58	38
1.0	10	2	69	60
1.7	10	3	60	28
3.0	10	3	45	16
7.0	10	3	36	14
1.0	20	3	49	33
1.0	20	2	63	52
1.7	20	2	51	33
3.0	20	2	42	24

<sup>a</sup> Analyzed by GLC and based on unrecovered starting material.

tution disappeared a 50:50 mixture of methylene and methyl substitution product being obtained. This shows that there must be an intrinsic difference between acetonitrile and methylene chloride as solvents for anodic cyanation, and that the additional complication of an emulsion system in the latter case probably has no influence of its own.

Current yields for the cyanations reported in Table 1 generally fall in the region between 20 and 40 % in both systems.<sup>8</sup> In order to study the influence upon product yields of changing the volume ratios between the two phases, 1,3-dimethoxybenzene was chosen as the substrate

for a series of such experiments. Table 2 shows that an increase of the aqueous phase at the expense of the organic one leads to decreasing current yields but leaves the material yields largely unchanged. For some reason, a higher concentration of phase transfer agent decreases both material and current yield.

A preparative experiment under the same conditions (2 F/mol of substrate, 10 mmol of phase transfer agent) as those given in Table 2, but with 50 mmol of substrate, led to the isolation of 2,4-dimethoxybenzonitrile in 61 % yield.

*Trimethoxybenzenes.* Table 3 shows products and yields from the emulsion electrolysis of the

Table 3. Anodic cyanation of trimethoxybenzenes. Electrolyte: Aqueous 1 M NaCN (100 ml), methylene chloride (100 ml), Bu<sub>4</sub>NSO<sub>4</sub>H (10 mmol), substrate (10 mmol).

Trimethoxybenzene	Products	Yield, %	
		Emulsion system <sup>b</sup>	CH <sub>3</sub> CN/ Et <sub>4</sub> NCN <sup>c</sup>
1,2,3-	2,6-Dimethoxybenzonitrile	28 <sup>a</sup>	86 <sup>a</sup>
	2,6-Dimethoxyterephthalonitrile	1.4 <sup>d</sup>	
1,3,4-	2,4-Dimethoxybenzonitrile	38 <sup>a</sup>	
	3,4-Dimethoxybenzonitrile	1 <sup>a</sup>	
1,3,5-	2,4,6-Trimethoxybenzonitrile	56 <sup>d, e, f</sup>	

<sup>b</sup> Analyzed by GLC and based on unrecovered starting material. <sup>c</sup> This work; 3 F/mol of substrate passed. <sup>d</sup> Ref. 8. <sup>e</sup> Isolated yield, based on unrecovered starting material. <sup>f</sup> With 20 mmol of phase transfer agent added, this yield drops to 40 %. <sup>f</sup> Dicyanation takes place to same extent (see text).

three trimethoxybenzenes. Again, we can establish the acetonitrile system as being the more selective one (only replacement of methoxyl group, no dicyanation).

**Dicyanation.** The cyanation reaction has previously been reported to be selective towards monocyanation, as would be expected in view of the deactivating effect of electron-withdrawing substituents upon anodic substitution.<sup>14,15</sup> However, prolonged electrolysis has been shown to give dicyanation products from anisole<sup>13</sup> and now a few other cases of dicyanation have been demonstrated (Tables 1 and 3). In order to find out the extent of this process, we electrolysed 2,4-dimethoxybenzonitrile by itself in the emulsion system until 3 F/mol of substrate had passed and found a 28 % material and 8 % current yield of 4,6-dimethoxyisophthalonitrile; in a similar experiment, 2,4,6-trimethoxybenzonitrile gave the corresponding dinitrile in 53 % material and 17 % current yield.

## EXPERIMENTS

**Materials.** Most chemicals used in this investigation are commercially available and have been used without further purification. The following substances have been synthesized by diazotization of the appropriate dimethoxyaniline followed by treatment with copper(I) cyanide:<sup>28</sup> 3,4-dimethoxybenzonitrile, yield 39 %, m.p. 65–67°C (lit. 67–68°C),<sup>27</sup> 3,5-dimethoxybenzonitrile, yield 15 %, m.p. 85–86°C (lit. 87–88°C),<sup>28</sup> and 2,5-dimethoxybenzonitrile, yield 25%, m.p. 81–82°C (lit. 80°C).<sup>29</sup> 2,6-Dimethoxybenzonitrile was synthesized from 1,3-dinitrobenzene<sup>30</sup> in 17 % yield, m.p. 119–120°C (lit. 117–118°C).<sup>30</sup>

**Electrolysis equipment.** Electrolyses were carried out in an open jacketed vessel, 300 ml in volume. The cell was equipped with a platinum foil anode (55 cm<sup>2</sup>) and a stainless steel cathode. A high-speed stirring device<sup>16</sup> was placed in the middle of the cell between the electrodes. Electrolyses were run at constant current maintained by a Radiak power supply.

**General electrolysis procedure.** The electrolyte consisted of 10 mmol of substrate, 100 ml of dichloromethane, 100 ml of 1 M sodium cyanide and 10 or 20 mmol of tetrabutylammonium hydrogen sulfate dissolved in 15 ml of water and neutralized with sodium hydroxide. Electrolyses were run at a constant current of 0.75 A, resulting in a current density of 0.014 A/cm<sup>2</sup>. Charge equivalent to 2, 3, or 6 F/mol was passed. The very efficient stirring kept the electrolyte well emulsified during the run. The potential drop across the cell varied between 12 and 20 V. When starting up the electrolysis the

stirrer had to be turned on for a few seconds and then off and left for half a minute and then turned on again in order to get the voltage over the cell to rise from the initial value of 4–5 V. This is probably due to a wetting phenomenon.

**General workup procedure.** After the stirrer had been switched off the two phases separated rapidly and the organic layer was evaporated to dryness. The residue was taken up in 15 ml of water and extracted with 3 × 20 ml of ether. The combined ether layers were dried over magnesium sulfate and reduced in volume to about 15 ml. Finally, products were analyzed by GLC using a 2 m × 3 mm 5 % neopentylglycol succinate column.

**1,2-Dimethoxybenzene.** Experiments were carried out according to the general procedure. Besides 2-methoxybenzonitrile and 3,4-dimethoxybenzonitrile three other products were found in less than 5 % total yield. MS analysis indicated that these products were 2,3-dimethoxybenzonitrile, one isomer of the addition product, dicyanodimethoxycyclohexadiene, and one isomer of dicyanoanisole. Yields are given in Table 1.

**1,3-Dimethoxybenzene.** Electrolyses were carried out according to the general procedure. During workup a solid, insoluble in ether, precipitated. After recrystallization from ethanol, the substance was shown to be 4,6-dimethoxyisophthalonitrile (see cyanation of 2,4-dimethoxybenzonitrile). The main product, 2,4-dimethoxybenzonitrile, was isolated and recrystallized from ligroin (b.p. 80–110°C), m.p. 90–91°C (lit.<sup>29</sup> 89°C). NMR and mass spectra were in accordance with the proposed structure. The crude product was also analysed according to the general workup procedure. Yields, determined by GLC, are given in Tables 1 and 2.

**1,4-Dimethoxybenzene.** Experiments were carried out according to the general procedure. GLC/MS analysis showed, besides 4-methoxybenzonitrile and 2,5-dimethoxybenzonitrile, two isomers of dicyanodimethoxycyclohexadiene. Yields are given in Table 1.

**1,2,3-Trimethoxybenzene.** Experiments followed the general procedure. The yield of the main product, 2,6-dimethoxyterephthalonitrile, precipitated. The substance was recrystallized from ethanol and then sublimed *in vacuo*. 2,6-Dimethoxyterephthalonitrile sublimed below the melting point. NMR:  $\delta$  4.0 (s, 6 H), 6.85 (s, 2 H). IR: Strong band at 2235 cm<sup>-1</sup>. MS: *m/e* (%), 189 (12), 188 (100); 187 (12); 145 (42); 131 (13); 128 (63). Elemental analysis: Calc.: C 63.8; H 4.26; N 14.9. Found: C 63.7; H 4.39; N 15.0.

**1,2,4-Trimethoxybenzene.** Experiments were carried out according to the general procedure. Yields are given in Table 3.

**1,3,5-Trimethoxybenzene.** Electrolyses were carried out according to the general procedure. The product, 2,4,6-trimethoxybenzonitrile, was extracted into ether. The solvent was evaporated and the residue was recrystallized from

ligroin (b.p. 80–110 °C), m.p. 143–144 °C (lit.<sup>21</sup> 143–144 °C). NMR, IR, and mass spectra were in accordance with this structure. During workup a solid precipitated that was recrystallized from ethanol. It was shown to be 2,4,6-trimethoxyisophthalonitrile (see cyanation of 2,4,6-trimethoxybenzonitrile). Yields are given in Table 3.

**2,4-Dimethoxybenzonitrile.** Electrolyses were run according to the general procedure. During workup a solid precipitated between the ethereal and aqueous layers and was collected by filtration. The product, 4,6-dimethoxyisophthalonitrile, was recrystallized from ethanol and sublimed *in vacuo*, m.p. 51–52 °C. NMR:  $\delta$  4.1 (s, 6 H), 7.0 (s, 1 H), 8.0 (s, 1 H). IR: Strong band at 2235 cm<sup>-1</sup>. MS: *m/e* (%), 189 (13); 188 (100); 187 (15); 159 (34); 158 (14); 145 (24). Elemental analysis: Calc.: C 63.8; H 4.26; N 14.9. Found: C 63.9; H 4.30; N 14.5.

**2,4,6-Trimethoxybenzonitrile.** Electrolyses were carried out according to the general procedure. The product precipitated as described for 4,6-dimethoxyisophthalonitrile and was recrystallized from ethanol. Prior to combustion analysis the substance was sublimed *in vacuo*. The yield of 2,4,6-trimethoxyisophthalonitrile, m.p. 250–1 °C, was 53 % (material) and 17 % (current). NMR:  $\delta$  4.05 (s, 6 H), 4.2 (s, 3 H), 6.7 (s, 1 H). IR: Strong band at 2235 cm<sup>-1</sup>. MS *m/e* (%), 219 (13); 218 (100); 217 (8); 175 (15). Elemental analysis: Calc.: C 60.6; H 4.59; N 13.1. Found: C 60.7; H 4.64; N 13.1.

***N,N*-Dimethylbenzylamine.** This compound was anodically cyanated in three different ways.

1. According to the general procedure, 10 mmol of substrate was electrolyzed with 10 mmol of tetrabutylammonium salt present. Charge equivalent of 3 F/mol was passed. Workup according to the general procedure and analysis by NMR and GLC/MS gave a 46:54 ratio of *N,N*-dimethylphenylglycinonitrile and *N*-benzyl-*N*-methylglycinonitrile.

When 50 mmol of substrate and 20 mmol of supporting electrolyte were electrolyzed as above, a 46 % yield of products was isolated in a current efficiency of 31 %. The isomer ratio was the same as above.

2. Electrolyses were run in a divided cell with 10 mmol of substrate and 20 mmol of tetrabutylammonium cyanide in 100 ml of methylene chloride as the anolyte. The catholyte consisted of 0.2 M tetrabutylammonium tetrafluoroborate in methylene chloride. A ceramic cup was used as a cell divider. Two platinum foil electrodes were used, the anode area being 60 cm<sup>2</sup>. A charge equivalent to 2 F/mol was passed at 0.3 A. Tetrabutylammonium fluoroborate (5 mmol) was added during electrolysis in order to increase the conductivity of the anolyte. Workup according to the general procedure followed by GLC analysis showed a 54:46 ratio of *N,N*-dimethylphenylglycinonitrile and *N*-benzyl-*N*-methylglycinonitrile.

3. Substrate (10 mmol) and tetrabutylam-

monium cyanide (20 mmol) in acetonitrile were electrolyzed at a platinum foil anode and a stainless steel cathode. Charge equivalent to 2 F/mol was passed at 0.75 A. Conventional workup and GLC analysis showed that substitution had taken place exclusively in methyl position.

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