Anodic Oxidations. VII.[1] Nuclear Cyanation of Methylanisoles

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Electrochemical oxidation of methylanisoles in methanol containing sodium cyanide was investigated. In the cases of ortho- and meta-substituted methylanisoles, nuclear cyanation took place preferentially. With *p*-methylanisole, side-chain methoxylation surpassed nuclear cyanation. The data obtained are compared with those of other electron-transfer reactions such as the anodic acetoxylation and the acetoxylation and chlorination by metal oxidizing agents. Factors controlling the competition between nuclear and side-chain substitution in alkyl aromatic compounds are ascribable to the degree of positive charge on the aromatic carbon atoms in the cation radicals as well as the nucleophilicity of attacking agents.

The electrochemical oxidation of alkyl aromatics has attracted considerable attention.[2] It is common to observe products resulting from substitution on both the aliphatic side chain and the aromatic nucleus. There appear to be at least two distinct mechanisms, one in which the substrate is oxidized in the primary electrode reaction, while the other in which the primary electron transfer is from either an anion or the solvent. If electron-donating groups such as methoxy are introduced on the aromatic ring, then the oxidation potential of substrates goes down and the former type of mechanism becomes predominant.[2g]

The oxidation of alkyl aromatic compounds by means of metal salts has also been studied extensively. Application of strong oxidants such as cobalt(III) or manganese(III) to substrates having relatively low oxidation potential causes a charge-transfer reaction involving aromatic cation radical intermediates, which gives side chain substitution products.[3] In the presence of relatively reactive nucleophiles such as chloride ion, nuclear substitution is observed together with side chain substitution.[3b]

The anodic cyanations of alkyl aromatic hydrocarbons such as toluene and tetralin were previously tried in methanol.[4] Side-chain methoxylation was the main reaction and small amounts of nuclear cyanation products were by-produced. The primary electrode process of this reaction is the oxidation of aromatic compounds to cationic species which subsequently react with nucleophiles.[5] There appear to be two essentially important means for favoring anodic cyanation: one is to lower the oxidation potential of organic compounds and the other is to increase the positive charge on any of the aromatic carbon atoms in anodically generated cationic species. If a suitable substituent is put on the aromatic ring, these two favorable factors will be satisfied and cyanation may well become the main reaction. We expected a methoxy group to be such a substituent. In the cases of *o*- and *m*-methylanisoles, aromatic cyanation became the main reaction. With *p*-methylanisole, side chain methoxylation was still predominant. In this article, factors controlling the relative prevalence of the two pathways leading to the nuclear cyanation and the side chain methoxylation are discussed.

Results

The anodic oxidation of *o*-methylanisole in methanol containing sodium cyanide was carried out under a nitrogen atmosphere at 25 ± 1°, with a constant current of 0.1 A. Four aromatic cyanation products, 4-methoxy-3-methyl-, 3-methoxy-4-methyl-, and 2-methoxy-3-methylbenzonitriles, and *o*-methylbenzonitrile, were formed together with a substantial amount of aromatic methoxylation product, 2,5-dimethoxytoluene. Table I summarizes the results of electrochemical reaction. It also contains the results of anodic cyanation in the acetonitrile solution of tetraethylammonium cyanide.

The electrochemical oxidation of *m*-methylanisole gave four ring cyanation products, 2-methoxy-6-methyl-, 4-methoxy-2-methyl-, and 2-methoxy-4-methylbenzonitriles, and *m*-methylbenzonitrile. Very small amounts of unidentified methoxylation products were by-produced. The reaction in acetonitrile gave the same type of products in poor yield.

Under the above conditions, *p*-methylanisole gave mono- and di-side-chain methoxylation products, *p*-methoxymethylanisole and *p*-methoxybenzaldehyde dimethyl acetal, together with three aromatic cyanation products, 2-methoxy-5-methyl- and 5-methoxy-2-methyl-benzonitriles and *p*-methylbenzonitrile, and a very small amount of side chain cyanation product, *p*-methoxybenzyl cyanide. The reaction in acetonitrile solution of tetraethylammonium cyanide yielded the same cyanation products. Methoxyl displacement by nitrile did not occur.

The current efficiency for these reactions was 60% or so and the remainder of the current would be consumed with the oxidation of cyanide ion. Cyanide ion discharges at the potentials used probably to produce a cyano radical, which might attack the coexisting cyanide ion to form cyanogen anion radical or dimerize to cyanogen.[5b]

Discussion

The cyanation reaction was first attributed to an ion discharge mechanism.[4a,6] However, as a result of recent investigations, there is general agreement so far as the aromatic compound is concerned. Several types of experimental evidence in favor of direct anodic oxidation of the substrate have been presented; they include voltammetric data, controlled potential electrolysis experiments, and results from product analyses.[5,7-9]

The nuclear cyanation and side chain oxidation of alkyl aromatic compounds are formally a 2-equiv change. Controlled potential coulometric data of the anodic cyanation of 2,5-dimethylfuran, 2,5-dimethylthiophene, and diphenylamines support this experimentally,[5c,8,9] although in the case of methylanisoles we were unable to use this technique because of increasing contamination of the anode surface by the electrolysis product. At least two types of cationic intermediates are conceivable: a cation radical produced by an initial one-electron oxidation[10] and a dication formed by either a single two-electron transfer[2a,c] or a disproportionation of initially produced cation radicals.[11,12] By analogy with the anodic pyridination of 9,10-diphenylanthracene[13] and the anodic hydroxylation of thianthrene,[11] a mechanism involving a cation radical intermediate is reasonable.[14] It is difficult to detect directly the cation radical as the intermediate under the strongly basic environments

Table I
Anodic Cyanation of Methylanisoles

Reactant (Registry no.)	Product	Current efficiency,[a] % NaCN in MeOH[b]	Et$_4$NCN in MeCN[b]	Position substd
o-Methylanisole	*o*-Methylbenzonitrile	0.4	9.1	1
(578-58-5)	4-Methoxy-3-methylbenzonitrile	47.2	7.1	4
	3-Methoxy-4-methylbenzonitrile	2.1	0.6	5
	2-Methoxy-3-methylbenzonitrile	7.3	6.3	6
	2,5-Dimethoxytoluene	4.0		4
m-Methylanisole	*m*-Methylbenzonitrile	0.7	0.9	1
(100-84-5)	2-Methoxy-6-methylbenzonitrile	11.4	3.2	2
	4-Methoxy-2-methylbenzonitrile	35.2	9.4	4
	2-Methoxy-4-methylbenzonitrile	15.8	6.2	6
p-Methylanisole	*p*-Methylbenzonitrile	5.4	8.2	1
(104-93-8)	2-Methoxy-5-methylbenzonitrile	17.4	13.0	2, 6
	5-Methoxy-2-methylbenzonitrile	1.8	1.9	3, 5
	p-Methoxybenzyl cyanide	Trace	Trace	Me
	p-Methoxymethylanisole	12.0		Me
	p-Anisaldehyde dimethyl acetal	24.0[c]		Me

[a] Based on 2e process. [b] Temperature, 25°; electricity, 1 F/mol. [c] Based on 4e process.

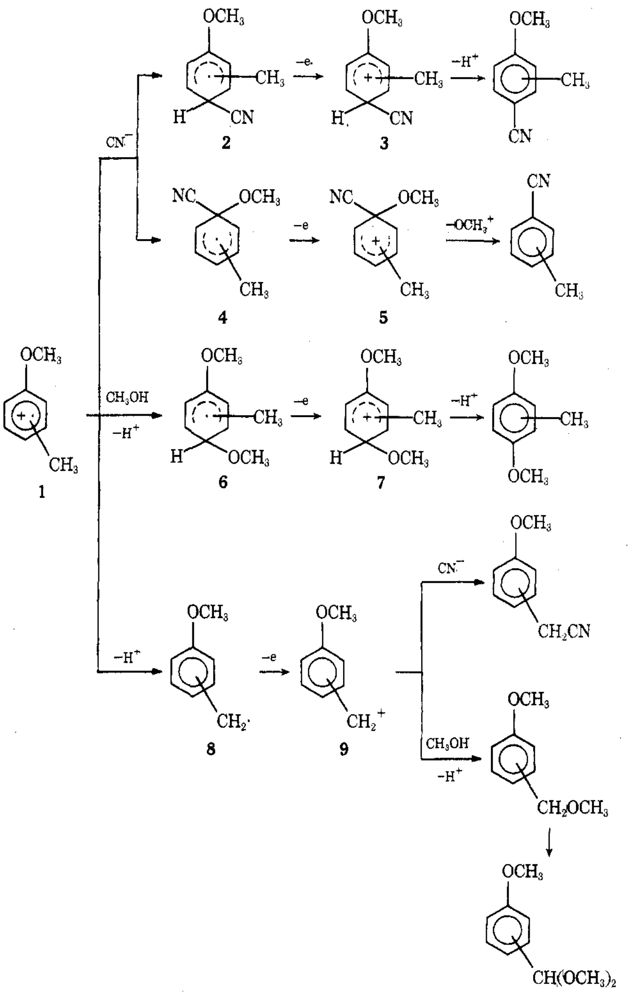
such as methanolic sodium cyanide. Even in weakly basic media such as acetonitrile–perchlorate, the cyclic polarogram of *p*-methylanisole does not give two oxidation peaks separately but gives a peak which corresponds to the transfer of two electrons; a proton peak is observed on the cathodic sweep.[17] The esr measurement of cobaltic acetate oxidation in trifluoroacetic acid, a very weakly basic medium, has shown the presence of the cation radical of *p*-methylanisole.[3b]

The mechanism shown in Scheme I would, therefore, be reasonable to account for the electrochemical oxidation of alkyl aromatics. The principal part of this mechanism is what we previously proposed for the anodic oxidation of 2,5-dimethylfuran[5c] and 2,5-dimethylthiophene[8] and is closely related to that proposed for the oxidation of toluene by cobaltic acetate.[3b] The anodically generated cation radical **1** is attacked by the cyanide ion (or methanol) to produce the radical **2** (or **6**), followed by further anodic oxidation and successive proton release, thus leading to the aromatic cyanation (in part methoxylation) products. Part of **1** should also undergo deprotonation to afford the usual radical intermediate **8**, which should eventually give rise to side-chain oxidation products.

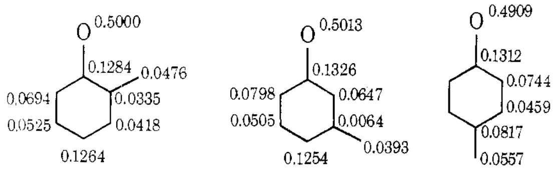
An alternative mechanism for side-chain oxidation is the ion discharge mechanism. Cyanide ion unquestionably discharges at the potentials used probably to produce a cyano radical, which might abstract a hydrogen atom from the side chain. However, cyanide ion oxidation would not relate directly with the side-chain methoxylation: if the anodically generated radicals abstract a hydrogen atom from the side chain of methylanisole, *o*- and *m*-methylanisoles as well as *p*-methylanisole should produce the side-chain methoxylation products.

In a previous paper of this series,[1] we demonstrated unambiguously that there are two essentially important stages for anodic cyanation of aromatic compounds: the first stage is the electrochemical oxidation of organic compounds to cation radicals and the second step is the combination reaction of the anodically generated cation radicals with cyanide anion. One can facilitate the former stage by lowering the oxidation potential of substrates by introducing the electron-donating groups such as methoxy on the aromatic nucleus. The second stage is apparently assisted by larger positive charge localized on the carbon atoms in the cation radicals formed. This latter stage is in fact essential; although both *o*- and *m*-methylanisoles have a higher oxidation potential than *p*-methylanisole,[18] their current efficiency in aromatic cyanation is even greater than that of the *p*-methyl isomer.

Scheme I



Nuclear Substitution. The remarkable reaction of cation radicals in the present electrolyte system is the attack of a nucleophile on the aromatic nucleus. This type of reaction is especially important with *o*- and *m*-methylanisole cation radicals. According to the proposed mechanism in Scheme I, it is to be expected that the carbon atoms of a higher positive charge in the cation radicals **1** would react more readily with a nucleophile. Net charge distributions calculated for methylanisole cation radicals by the ω technique[22] show much the same distribution pattern as that of displacement products of aromatic hydrogen by cyanide ion.[23]



An another possible reaction of alkyl aromatic cation radicals is a loss of an α proton, which competes with an attack of a nucleophile on the aromatic nucleus. This competitive reaction was indeed found to be important in the case of *p*-methylanisole. The relative extent of nuclear oxidation is directly related to the degree of positive charge on the carbon atom with an aromatic hydrogen relative to that in the other positions of the cation radical. The relative degree of positive charge on the carbon atoms with an aromatic hydrogen in *p*-methylanisole cation radical is less than that in *o*- and *m*-methylanisole cation radicals. Therefore, the anodic oxidation of *o*- and *m*-methylanisoles occurs almost exclusively on the aromatic nucleus, whereas in *p*-methylanisole cation radical, a proton loss competes with a nuclear attack.

The nuclear attack is important when the relatively reactive nucleophiles such as cyanide or chloride ion are used. Thus, while the oxidation of *p*-methylanisole gave only small amounts of nuclear acetoxylation products in the presence of acetate ion,[2c,24] it gave nuclear cyanation products in considerable yields in the presence of cyanide ion. Similarly, the oxidation of toluene with cobaltic acetate gave no measurable nuclear acetoxylation in the presence of acetate ion, whereas it gave substantial yields of nuclear chlorination products in the presence of high chloride ion concentrations.[3b] Analogous results were also obtained with 2-methylnaphthalene. The anodic acetoxylation of toluene is interpreted in the same manner. The relative ratio of nuclear acetoxylation to side-chain acetoxylation was 2.5 in acetic acid containing acetate ion,[2a] whereas it decreased to 0.1 in acetic acid containing nitrate ion.[2d] For anisole, ethylbenzene, and tert-butylbenzene, this tendency is more remarkable. It has been found that the presence of acetate ion is essential for nuclear acetoxylation to occur; no reaction occurs if tosylate or perchlorate is substituted, even with acetic acid as the solvent.[2c]

To check the possibility that methoxymethylbenzonitrile may be produced by anodic cyanation of dimethoxytoluene initially obtained by anodic methoxylation of methylanisole, the anodic cyanation of 3,4-dimethoxytoluene was investigated. The reaction product was not 2-methoxy-5-methylbenzonitrile but 2-methoxy-4-methylbenzonitrile. It is, therefore, concluded that 2-methoxy-5-methylbenzonitrile is produced by the direct substitution of aromatic hydrogen of *p*-methylanisole by cyanide ion.

Side-Chain Substitution. A possible reaction of alkyl aromatic cation radicals is the proton expulsion from the side chain alkyl group.[3b,8] The benzylic radical formed is then rapidly oxidized to the corresponding benzylic cation.[2f] *p*-Methoxybenzyl cation combined predominantly with the solvent methanol to give *p*-methoxymethylanisole; the side-chain cyanation product, *p*-methoxybenzyl cyanide, was formed only in trace amounts. To ascertain this preference of the cation for methanol, the competitive reactions of solvent methanol and sodium cyanide with *p*-chloromethylanisole were investigated. it is known that this chloride readily produces the *p*-methoxybenzyl cation.[25] Product analysis showed that *p*-methoxymethylanisole was the major product, in agreement with the results of anodic oxidation.

p-Anisaldehyde dimethyl acetal is produced by the further oxidation of methoxymethylanisole.[26]

Experimental Section

The electrochemical and spectroscopic instrumentation and techniques were as previously described.[5c]

Materials. Methanol was purified as previously described.[5c] Reagent grade sodium cyanide was used with no purification other than drying. Methylanisoles and tolunitriles were obtained commercially and were purified by distillation before use.

Tetraethylammonium cyanide was prepared according to the method given by Andreades and Zahnow.[5b]

The following reference materials were prepared according to the literature: 2-methoxy-3-methylbenzonitrile,[27] 2-methoxy-4-methylbenzonitrile,[28] 2-methoxy-5-methylbenzonitrile,[30] 2-methoxy-6-methylbenzonitrile,[31] 3-methoxy-2-methylbenzonitrile,[32] 3-methoxy-4-methylbenzonitrile,[33] 4-methoxy-2-methylbenzonitrile,[34] 4-methoxy-3-methylbenzonitrile,[35] 5-methoxy-2-methylbenzonitrile,[36] *p*-methoxybenzyl cyanide,[37] 2,3-,[38] 2,4-,[39,] 2,5-,[40] 2,6-,[41] 3,4-,[42] and 3,5-dimethoxytoluenes,[43] *p*-methoxymethylanisole,[44] *p*-anisaldehyde dimethyl acetal,[45] 2- and 3-acetoxy-4-methylanisoles,[3a] and *p*-methoxybenzyl acetate.[46]

Anodic Cyanation. A methanolic solution (200 ml) of methylanisole (14.6 g, 0.12 mol) and sodium cyanide (5.9 g, 0.12 mol) was electrolyzed at 25°, with a constant current of 0.1 A at 13–19 V, until 1 F/mol of charge was passed through the solution. The catholyte was a methanol solution of sodium cyanide. The electrolyzed mixture was treated as usual.[5c] The products were analyzed by vpc, the column packing being PEG 6000.

Each product was separated in pure form by preparative vpc and the ir, nmr, and mass spectra of the products were compared with those of the corresponding authentic sample.

Anodic Acetoxylation of *p*-Methylanisole in Methanol. The anolyte was made up of 19.5 g (0.16 mol) of *p*-methylanisole and 13.1 g (0.16 mol) of sodium acetate in 200 ml of methanol. The catholyte was a methanolic solution of sodium acetate (0.8 *M*). The electrolysis was carried out at 25°, with a constant current of 0.1 A until 1 F/mol had passed through the electrolyte. The solution was then dropped into a vigorously stirred slurry of sodium bicarbonate in water. The organic product was taken up in ether, dried over sodium sulfate, filtered, and stripped on a rotary evaporator. The residue was then analyzed by glc using PEG 6000 column. The following materials were obtained: *p*-methylanisole recovered (8.53 g, 0.070 mol), 2-acetoxy-4-methylanisole (0.36 g, 0.002 mol; current efficiency, 2.5% based on 2e process), *p*-methoxybenzyl acetate (0.25 g, 0.001 mol; current efficiency, 1.3%), *p*-methoxymethylanisole (3.94 g, 0.026 mol; current efficiency, 32.5%), and anisaldehyde dimethyl acetal (1.01 g, 0.006 mol; current efficiency, 15.0% based on 4e process).

Registry No.—*o*-Methylbenzonitrile, 529-19-1; *m*-methylbenzonitrile, 620-22-4; *p*-methylbenzonitrile, 104-85-8; *p*-methoxybenzyl cyanide, 104-47-2; 2-methoxy-3-methylbenzonitrile, 53078-68-5; 2-methoxy-4-methylbenzonitrile, 53078-69-6; 2-methoxy-5-methylbenzonitrile, 53078-70-9; 2-methoxy-6-methylbenzonitrile, 53005-44-0; 3-methoxy-4-methylbenzonitrile, 3556-60-3; 4-methoxy-2-methylbenzonitrile, 21883-13-6; 4-methoxy-3-methylbenzonitrile, 53078-71-0; 5-methoxy-2-methylbenzonitrile, 22246-19-1; *p*-methoxymethylanisole, 1515-81-7; 2,3-dimethoxytoluene, 4463-33-6; 2,4-dimethoxytoluene, 38064-90-3; 2,5-dimethoxytoluene, 24599-58-4; 2,6-dimethoxytoluene, 5673-07-4; 3,4-dimetholytoluene, 494-99-5; 3,5-dimethoxytoluene, 4179-19-5; *p*-methoxybenzaldehyde dimethyl acetal, 2186-91-7; sodium cyanide, 143-33-9.

Supplementary Material Available. The ir, nmr, and mass spectra of the products will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 ×

148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-63.

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Reaction of Isocyanides with Thio Acids[1]

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Reaction of isocyanides, **1**, with thiocarboxylic acids, **2**, have been found to give novel *N*-thioformyl-*N*-acylamides, **3**, and in certain instances, thioformamide **4.** The formation of **3** thus represents a departure from the usual reaction of mercaptans or carboxylic acids with **1.** The former usually give simple alkylthio α adducts, while formamide and acid anhydride formation results from reaction of the latter with **1.** When phosphorus thio acids are herein substituted for **2**, simple α adducts **5** are first formed which, *via* measurable first-order kinetics, are transformed to novel, stable *N*-thioformyl-*N*-phosphoramides, **6.** The reaction rates are shown to depend on the nature of both the phosphorus thio acid and the isocyanide, with no **6** evident from reaction of phosphinodithioic acid with **1.** Finally, reaction of dithiocarbamic acids (*via* their salts) with **1**, is shown to give the α adduct **7** in a reaction that is largely reversible at high temperatures.

The reaction of mercaptans with organic isocyanides has been shown to give α adducts or isothiocyanates, depending upon the reactants, catalyst, and reaction systems.[2] On the other hand, α adducts arising from carboxylic acids are unstable, with formamide and acid anhydrides as the products isolated.[3]

It was therefore of interest to study the reaction of isocyanides with thio acids. These latter materials have chemi-