Anodic Methoxylation of Tertiary Amines

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Anodic oxidation of N,N-dimethylbenzylamine has been carried out in methanolic solutions in order to examine the anodic methoxylation process. The conclusion is drawn that, while the amine does react directly at the anode, this is not a necessary initial step in methoxylation. A reaction scheme is proposed which involves direct anodic discharge of methoxide to methoxyl radical, followed by reaction of methoxyl with amine.

Inoue, *et al.*,[1-5] studied the anodic methoxylation of a number of aromatic compounds. They suggested a mechanism involving discharge of methoxide ions at the anode to form neutral radicals which could abstract hydrogen atoms from the substrate. The resulting radicals could then be anodically oxidized to cations which could react with methoxide ions to form ethers. Also noted was the possibility that neutral hydrocarbon radicals could react with anodically generated methoxyl radicals.

Weinberg and Brown[6] have suggested that anodic methoxylation of tertiary amines occurs by direct reaction of the substrate at the electrode. The reaction of N,N-dimethylbenzylamine in NaOH–methanol is said to involve adsorption of the amine on the anode, followed by the loss of two electrons and a proton to form, predominantly, $PhCH_2N(CH_3)CH_2^+$, which reacts with methanol to form an ether. The unexpected importance of N-methyl, rather than benzyl, substitution was attributed, in part, to the effect of adsorption.

We have had experience with similar systems which makes this mechanism appear incorrect. Using methanol with $NaClO_4$ supporting electrolyte in a divided cell with controlled anode potential, we find only protonated starting material and protonated secondary amine produced by dealkylation of the starting material. To determine whether our use of a neutral salt supporting electrolyte, in contrast with the base previously reported, is responsible for the difference in the products, we have examined the electrochemical behavior of N,N-dimethylbenzylamine in solutions of KOH and KOMe in methanol. We wish to report the results of these experiments, referred to as KOH and KOMe electrolyses, respectively, and to suggest a reaction scheme to account for these results.

Experimental Section

Large-scale electrolyses were carried out in two- or three-compartment, H-type cells with glass frits separating the compartments. An electronic potentiostat was used with a platinum anode and cathode and a silver–0.10 *M* $AgNO_3$–methanol reference electrode. Reagent grade methanol was used; oxygen was removed by sparging with nitrogen.

Experiments with $NaClO_4$ supporting electrolyte were made using 0.25 *M* salt at a potential of +0.70 v *vs.* the reference electrode. These electrolyses were allowed to continue until the current had dropped to a small, nearly constant value. Experiments with basic electrolytes were made in 1 *M* KOH or KOMe, with 6.6 mmoles of N,N-dimethylbenzylamine in about 125 ml of anolyte. The control potential was adjusted to give a current density of approximately 4 ma/cm^2, typically requiring an anode to reference electrode potential of 1.00 to 1.25 v. Electrolyses, run at 25°, were continued until 3 to 5 faradays of charge were passed per mole of starting amine.

Current–potential curves were taken by using a two-compartment cell with a platinum electrode in the cathode compartment and the Ag–$AgNO_3$ reference electrode, a perforated cylindrical platinum electrode having a combined inner and outer area of 11 cm^2, and a magnetic stirring bar in the anode compartment. Anode potential was controlled by a potentiostat, care being taken to ascertain that the output limits of the instrument were not exceeded. Systems examined were 0.3 *M* $NaClO_4$–MeOH, 1 *M* KOH–MeOH, 1 *M* KOMe–MeOH, and 0.3 *M* KOMe–MeOH. Current was measured as a function of anode-reference potential in the range of 0 to 0.8 v using approximately 25 m*M* amine concentrations except in the case of 0.3 *M* KOMe, for which concentration was increased to increments from 75 to 600 m*M*.

Product analysis utilized thermal conductivity and flame ionization gas chromatography with Dowfax 9N9-NaOH on Chromasorb W at 175°, silicone oil on Chromosorb P at 100°, and diethylene glycol succinate on Diatoport S at 135°. A picrate was made of the KOH electrolysis product. After recrystallization, it melted at 93°, compared with 93–94° for a valid sample and 93° in the literature.[7]

Samples for nmr examination were prepared by removing volatile components of the reaction mixture at a pressure of about 1 mm and trapping them at liquid nitrogen temperature. This yielded a basic solution and a solid residue, hereafter called the original residue. The solution was neutralized and the volatiles again removed. The resulting residue was taken into CD_3CN. To this was added a solution prepared by extracting the original solid residue with ether, neutralizing, removing the ether, and dissolving the residue in CD_3CN. The combined solution was shaken with base and dried over a 3-A molecular sieve. Solutions made by further extracting the original residue with acetonitrile and treating as above were also examined.

Results and Discussion

Average recoveries of products from four runs in 1 *M* KOH disclosed only 69.3 mole % of starting material, 8.8% of N-methylbenzylamine, and small amounts of dimethylamine and benzaldehyde. In 1 *M* KOMe, 32% of starting amine and 6% N-methylbenzylamine were recovered. Nmr examination of products recovered from KOH electrolysis gave spectra consistent with a mixture of N-methyl- and N,N-dimethylbenzylamines but with no evidence of methoxylation. Similar examination of products from KOMe electrolysis did give evidence of methoxylation, estimated from nmr evidence to be 5 to 10%

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[1] T. Inoue, K. Koyama, T. Matsuoka, K. Matsuoka, and S. Tsutsumi, *Kogyo Kagaku Zasshi*, **66**, 1659 (1963).

[2] T. Inoue, K. Koyama, T. Matsuoka, K. Matsuoka, and S. Tsutsumi, *Tetrahedron Letters*, 1409 (1963).

[3] T. Inoue, K. Koyama, and S. Tsutsumi, *Bull. Chem. Soc. Japan*, **37**, 1597 (1964).

[4] T. Inoue and S. Tsutsumi, *ibid.*, **38**, 661 (1965).

[5] T. Inoue, K. Koyama, T. Matsuoka, and S. Tsutsumi, *ibid.*, **40**, 162 (1967).

[6] N. L. Weinberg and E. A. Brown, *J. Org. Chem.*, **31**, 4054 (1966).

[7] "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Co., 1960, p 183.

of starting amine. Chemical shifts are given in Table I; control values for the ethers are from the literature.[6] In addition, there was a chromatographic peak, from the KOMe electrolysis only, following that of starting material, which may have been due to methoxylated amine.

TABLE I
RESULTS FROM NMR EXAMINATION OF KOMe ELECTROLYSIS PRODUCTS

Type of Proton	Control, τ	Unknown, τ
N-Methyl of starting material	7.83	7.80
N-Methyl of $PhCH_2NMeCH_2OMe$	7.71	7.80
N-Methyl of $PhCH(OMe)NMe_2$	7.82	7.80
Methoxy methyl of $PhCH_2NMeCH_2OMe$	6.87	6.94
Methoxy methyl of $PhCH(OMe)NMe_2$	6.75	6.74
Benzyl of starting material	6.60	6.65
Benzyl of $PhCH_2NHMe$	6.38	6.38
Benzyl of $PhCH_2NMeCH_2OMe$	6.10	6.18
N-CH of $PhCH_2NMeCH_2OMe$	6.37	6.34

We find that with KOH in a divided cell, nearly 80% of the starting amine is recovered, either unchanged or dealkylated, and that no evidence of methoxylation could be found. However, with KOMe, rather than KOH (but with other conditions the same) only about 32% of starting amine is recovered and methoxylation does occur. This indicates that methoxide ion is necessary for methoxylation.

It may be noted that in all of the work cited, methoxide was present. In most cases, it was deliberately added.[1-3,5] In others,[4,6] reactions were carried out in undivided cells with KOH initially present. Cathodic discharge of potassium ions would produce methoxide which would then be available at the anode. In one case, NH_4Br was substituted for KOMe in the oxidation of stilbene and no methoxylation occurred.[5]

All of the current-potential curves were conventional in shape; plotting current as ordinate *vs.* potential they showed gradually increasing slopes from 0 v. The curves obtained for $NaClO_4$–MeOH solutions with and without amine began to diverge above about 0.30 v. With 1 *M* KOH or KOMe and 25 m*M* amine, however, addition of amine produced little or no change up to 0.8 v, corresponding to 3 to 5 ma/cm^2. However, with 0.57 *M* amine and 0.3 *M* KOMe, the curves diverged above 0.30 v.

Our current-potential curve for methanol–$NaClO_4$ shows that N,N-dimethylbenzylamine reacts above 0.3 v under the conditions of these experiments. However, when hydroxide or methoxide is present, anion discharge is occurring at the same potential. The current-potential curve for KOMe (0.3 *M*)–amine (0.57 *M*) indicates that, for the conditions used by Weinberg and Brown, amine was reacting directly at the anode. However, the current efficiency for amine oxidation would be low. At the current densities used, there may have been some direct discharge of solvent as well.

In our current-voltage experiments, failure to see an increase in current when amine is added to a 1 *M* KOMe solution, even though the potentiostat was capable of furnishing much more power, indicates that, under these conditions, the limiting current for methoxide discharge had apparently not been exceeded; the current efficiency for the amine reaction would accordingly be very low. Nevertheless, in spite of the fact that very little amine was reacting directly at the electrode, a considerable consumption of amine occurred in the large-scale experiments. We feel that this indicates that the initial step in anodic methoxylation of aliphatic amines involves, not anodic oxidation of amine, but discharge of methoxide to methoxyl radical. We propose the scheme outlined in eq 1–4.

$$CH_3O^- \xrightarrow{\text{anode}} CH_3O\cdot + e^- \qquad (1)$$

$$CH_3O\cdot + PhCH_2NMe_2 \longrightarrow PhCH_2NMeCH_2\cdot\ (I) + PhCHNMe_2\ (II) + CH_3OH \qquad (2)$$

$$\text{I or II} \xrightarrow{\text{anode}} PhCH_2NMeCH_2^+\ (III)\ \text{or}\ Ph\overset{+}{C}HNMe_2\ (IV) + e^- \qquad (3)$$

$$\text{III or IV} + CH_3O^- \longrightarrow PhCH_2NMeCH_2OMe\ (V)\ \text{or}\ PhCH(OMe)NMe_2\ (VI) \qquad (4)$$

Compound V was the predominant methoxylation product, both in our work and that of Weinberg and Brown. This could happen, as suggested by them, because of the greater stability of II relative to I, causing the anodic oxidation of I to predominate. Adsorption of the intermediate on the electrode may also be important. This reaction scheme is analogous to that previously suggested by Inoue, *et al.* It is recognized that a number of unidentified products from reaction of methoxyl radicals with amine, *e.g.*, substituted ethylenediamines and N-oxides, might be formed.

Registry No.—N,N-Dimethylbenzylamine, 103-83-3; KOH, 1310-58-3; KOMe, 865-33-8.

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