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# The Electrochemical Polyalkoxylation of *N,N*-Dimethylformamide

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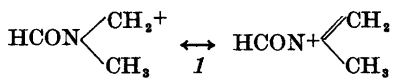
Anodic oxidation of *N,N*-dimethylformamide in methanol or ethanol, carried out until 4 F mol$^{-1}$ of substrate has been passed, yields a mixture of *N*-alkoxymethyl-*N*-methylformamide, *N,N*-bis(alkoxymethyl)formamide, *N*-dialkoxymethyl-*N*-methylformamide and *N*-alkoxymethyl - *N* - dialkoxymethylformamide. Two secondary products, *N*-alkoxymethylformamide and *N*-methylformamide, are probably formed by acid catalyzed decomposition of the primary products. The same products are also obtained by oxidation of *N*-alkoxymethyl-*N*-methylformamide. At a platinum anode the yields of the products are 60 – 70 %. Considerably lower yields are obtained at a graphite anode.

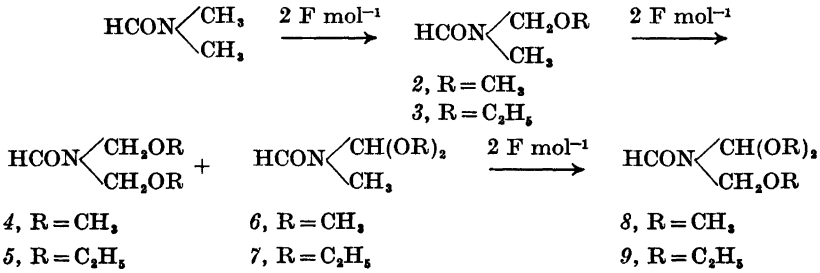
The anodic oxidation of *N,N*-dimethylformamide in methanol at either a platinum or a carbon anode proceeds smoothly to afford high yields (85 – 100 %) of *N*-methyl-*N*-methoxymethylformamide,[1,2] and the reaction has been run successfully on a larger scale.[3] With a quaternary ammonium fluoroborate, which requires a very high anodic potential for oxidation,[4] as the supporting electrolyte the mechanism is unambiguous and involves, in sequence, an electron transfer, a proton transfer and an additional electron transfer to give the product-forming, cationic intermediate, *1*.[2]



The facility of this monoalkoxylation reaction has aroused interest in the possibility of effecting further anodic oxidation in these systems to give di- and trialkoxylation products. In the present study polymethoxylation and polyethoxylation reactions have been explored starting both with *N,N*-dimethylformamide and with its monoalkoxylation product.

## RESULTS AND DISCUSSION

The polyalkoxylation products obtained on extensive anodic oxidation of *N,N*-dimethylformamide (DMF) or its monoalkoxylation product are shown in Scheme 1. Two degradation products, *N*-alkoxymethylformamide (*10* or *11*) and *N*-methylformamide (*12*) are also obtained. The genesis of



*Scheme 1.*

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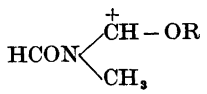
these degradation products is not certain. There is some evidence that thermal decomposition is not responsible. A solution containing both *9* and *11* was analyzed by GLC, first with the column at 160 °C, the thermal conductivity detector at 227 °C and the injection port at 215 °C and then with the column at 130 °C, the detector at 155 °C and the injection port at 155 °C. At these two very different sets of thermal conditions the observed ratios, *9*/*11*, were essentially unchanged. Therefore, these products, *10* or *11* and *12*, probably result from acid catalyzed decomposition of the alkoxylation products shown in Scheme 1. It is known that *N*-alkoxymethylamides are dealkylated in the presence of acid and moisture, and it has been shown that some acid is produced during anodic oxidations with fluoroborate supporting electrolytes.[5] There is the further likelihood that compounds containing a *gem*-dialkoxymethyl group are more subject to attack and that *6* and *7* are the more probable precursors of *12* and that *8* and *9* are the more probable precursors of *10* and *11*, respectively. Proof for this supposition is, however, lacking.

The product yields obtained on constant current polyalkoxylation of DMF or an alkoxylated DMF are assembled in Tables 1 and 2. Table 1 presents the results for methoxylation and Table 2 indicates the products obtained on ethoxylation. The effect of the anode material was unanticipated and is significant. Graphite, which permits high yields in the monomethoxylation of DMF,[3] is unsuitable as an anode for polyalkoxylation. No obvious explanation for this phenomenon is available.

The ratio of *vic*-dialkoxylation to *gem*-dialkoxylation, *4*/*6* or *5*/*7*, is of interest. On a purely statistical basis a ratio of 1.5 would be expected, since the monoalkoxylation product, *2* or *3*, has three hydrogens in the position leading to *vic*-substitution and two hydrogens in the position leading to *gem*-substitution. Opposed to this is the fact that of the two possible cationic intermediates, *13* is the more stable because of the additional possibility for charge delocalization provided by the alkoxy group. This would be expected to lower



*13*

the values of the ratios obtained. The observed ratios were 1.2 and 0.98 (Table 1) for the

*Table 1.* Product yields from the constant current (3 A), anodic oxidation of DMF (100 mmol) or *N*-methoxymethyl-*N*-methylformamide (100 mmol), *2*, in 0.14 M $Bu_4NBF_4$/MeOH (140 ml).

| Substrate | Anode | F mol$^{-1}$ | Yield/mmol | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *2* | *4* | *6* | *8* | *10* | *12* |
| DMF | Pt | 4 | 35.8 | 17.8 | 14.8 | 5.6 | 7.8 | 13.5 |
| *2* | Pt | 2 | 42.4 | 17.6 | 17.9 | 6.0 | 6.1 | 11.5 |
| *2* | C | 2 | 78.7 | 6.7 | 4.6 | 0.2 | 0.9 | 14.9 |

*Table 2.* Product yields from the constant current (3 A), anodic oxidation of DMF, *N*-ethoxymethyl-*N*-methylformamide, *3*, or *N*,*N*-bis(ethoxymethyl)formamide, *5*, in 0.35 M $Et_4NBF_4$/EtOH (140 ml).

| Substrate | mmol | Anode | F mol$^{-1}$ | Yield/mmol | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *3* | *5* | *7* | *9* | *11* | *12* |
| DMF | 200 | Pt | 4 | 53.0 | 37.4 | 47.9 | 5.3 | 22.7 | 21.2 |
| *3* | 100 | Pt[a] | 2 | 32.1 | 17.8 | 25.4 | 5.8 | 9.8 | 8.8 |
| *3* | 101 | C | 2 | 70.3 | 6.1 | 2.2 | – | 1.2 | 23.7 |
| *5* | 95.6 | Pt | 2 | – | 71.1 | – | 0.5 | 16.6 | – |

[a] Carried out at a constant current of 2 A.

methoxylation reaction and 0.78 and 0.70 (Table 2) for the ethoxylation reaction. These values are qualitatively reasonable and in accord with *a priori* considerations which suggest that the ratios should be lower than 1.5. However, the values obtained are very probably perturbed by the formation of two decomposition products, *N*-alkoxymethylformamide and *N*-methylformamide, in these reactions. Since the relative stabilities of *4* and *6* or *5* and *7* and their immediate precursors are not known, the impact of these decomposition reactions on the values of the observed ratios cannot be assessed quantitatively.

The last entry in Table 2, which reports the results obtained on attempted anodic oxidation of 95.6 mmol of *N,N*-bis(ethoxymethyl)-formamide, *5*, is instructive. Even though enough charge was passed to completely convert *5* to the triethoxy compound, *9*, only 0.5 mmol of *9* was obtained. In addition 16.6 mmol of *N*-ethoxymethylformamide, *11*, a degradation product, was formed, and 71.1 mmol (74.4 %) of *5* was recovered unchanged. This suggests that, contrary to *a priori* expectations, the *gem*-diethoxy compound, *7*, rather than *5*, is the more probable precursor of *9*.

Three of the ethoxylation products, *5*, *7* and *9*, shown in Scheme 1 are new compounds requiring some verification of the assigned structures. The *vic*-diethoxy compound, *5*, was isolated from an electrolysis reaction mixture by GLC and prepared by two independent non-electrolytic methods. The first preparation was from formamide, sodium hydride and ethyl chloromethyl ether following the procedure developed by Schöllkopf and Beckhaus [6] for the preparation of *N,N*-bis-(methoxymethyl)formamide. This preparation led to a complex mixture from which the desired product was isolated in poor yield by GLC.

A more satisfactory preparation of *5* involved the reaction of *N*-ethoxymethylformamide, *11*, first with sodium hydride and then with ethyl chloromethyl ether. With this method *5* was obtained in good yield and was purified by distillation. The necessary starting material, *11*, which is also a decomposition product formed in the electrochemical reaction (Table 2), had been prepared previously by both a chemical and an electrochemical method,[7] and the present study resulted in a somewhat improved procedure for its preparation.

The structure of *5*, isolated from the electrochemical reaction, follows from its NMR and the identity of its infrared spectrum and GLC retention time with that of *5* synthesized chemically. Reaction of *5* with pentamethylbenzene using the amidoalkylation procedure developed previously [8] gives *N,N*-bis(pentamethylbenzyl)formamide, *14*. The structure of *14* follows from the fact that it can also be prepared by amidoalkylating pentamethylbenzene with *11* to obtain *N*-pentamethylbenzyl formamide, *15*,[9] and then alkylating *15* with pentamethylbenzyl chloride to give *14*.

The *gem*-diethoxy compound, *7*, could not be separated from the electrolysis reaction in a pure state by GLC. The best sample obtained was shown by GLC analysis to consist of 92 % *7* and 8 % *11*, and the results obtained on elemental analysis (C, H and N) are in accord with this composition. Further confirmation for the structure of *7* is provided by NMR analysis of this same sample.

The triethoxy compound, *9*, was also isolated from an electrolysis reaction by GLC. The structural assignment is based on its NMR spectrum and its mass spectrum.

The structural assignments for the methoxylation products are based largely on mass spectra determined in combination with GLC. The known *vic*-dimethoxy compound,[6] *4*, and *10* were isolated from electrolysis reaction mixtures by preparative GLC, and these structures were confirmed with NMR spectra. The dimethoxy compound *6*, and the trimethoxy compound, *8*, decomposed during preparative GLC.

## EXPERIMENTAL

The experiments on methoxylation were carried out at the University of Lund in Lund, Sweden, and the ethoxylation experiments were performed at the Sprague Research and Development Center, North Adams, Massachusetts, U.S.A. Since there were differences in details and in the instrumentation used in the two locations, the experimental procedures will be described separately.

*Electrochemical methoxylation.* The electrolyses were carried out in a water-jacketed cell with no separation of anode and cathode compartments using a platinum anode (area 7.25 $cm^2$) or a graphite anode (area 7.25 $cm^2$) and a

platinum cathode. The electrolyte was made up from the substrate (100 mmol), $Bu_4NBF_4$ (20 mmol) and anhydrous methanol (140 ml). It is important to remove acidic residue in $Bu_4NBF_4$ by washing with water followed by drying. The electrolyses were run with a constant current of 3 A (25–30 V) and at a temperature of approximately 35 °C. The reaction mixtures were analyzed by GLC on a 2 m × 0.3 cm 10 % Carbowax on Supelcoport (80–100 mesh) column using a Hewlett-Packard HP-5830 gas chromatograph. Yields of products were determined by integration of the GLC peak areas and comparison with a reference compound.

From a reaction mixture it was possible to isolate products *4* and *10* by preparative GLC on a 6 m × 1 cm 15 % Carbowax on Chromosorb A (45–60 mesh) column using an Aerograph Autoprep A-700 gas chromatograph. *6* and *8* decomposed under preparative GLC conditions. The identification of *4* and *10* was based on NMR and MS data. The structures *6* and *8* are in accordance with the MS data obtained from GLC in combination with MS. $^1$H NMR spectra were recorded on a Jeol MH 100 instrument using $CDCl_3$ as solvent. The following data were obtained for *4* and *10*.

*4*: $\delta$ 3.34 and 3.37 (6 H, s, $CH_3O$), 4.73 and 4.88 (4 H, s, $CH_2$), 8.43 (1 H, s, HCO).

*10*: $\delta$ 3.33 and 3.37 (3 H, s, $CH_3O$), 4.61 and 4.73 (2 H, d, $CH_2$), 6.60 (1 H, broad t, NH). 8.17 and 8.35 (1 H, s, HCO).

Mass spectra were recorded on an LKB-9000 instrument at 70 eV and gave the following data.

*4* (M 133): *m/e* 102 (10 % rel. int.), 101 (19), 88 (23), 45 (100), 42 (23), 29 (12).

*6* (M 133): *m/e* 102 (21), 75 (100), 73 (12), 60 (17), 59 (37), 58 (12), 47 (16), 43 (13), 42 (77), 31 (47), 30 (28), 29 (40).

*8* (M 163): *m/e* 75 (64), 73 (11), 60 (27), 59 (11), 45 (46), 44 (16), 31 (92), 30 (21), 29 (100).

*10* (M 89): *m/e* 74 (14), 59 (8), 58 (14), 45 (9), 31 (51), 30 (27), 29 (100).

*Electrochemical ethoxylation.* The electrolysis cell was a water-jacketed, 200 ml beaker fitted with a magnetic stirring bar and a Teflon cover to which was attached the appropriate electrode assembly. In the experiments with a platinum anode the electrodes were two pieces of platinum, 0.25 mm thick and 2.5 cm wide immersed to a depth of 5 cm and at a separation of 2 cm. When a carbon anode was used, the above platinum electrodes were interconnected to form a dual cathode, and a graphite rod, 0.6 cm in diameter and immersed to a depth of 5 cm was placed between them as the anode. A typical electrolysis procedure was the following. A suspension of $Et_4NBF_4$ (50 mmol) in a solution of redistilled DMF (200 mmol) in anhydrous ethanol (140 ml) was electrolyzed at a constant current of 3 A at platinum electrodes with magnetic stirring and water cooling. After the passage of 0.8 F the contents of the cell were transferred to a 1 l flask with the aid of ether, and a large volume of ether was added. After standing overnight the mixture was filtered with suction yielding 10 g of recovered $Et_4NBF_4$. The filtrate was distilled from a 30 °C water bath at a pressure of 80–100 mmHg through a Vigreux column, and the residue was made up to 50 ml with ether for GLC analysis. The products shown in Table 2 were determined on a Varian 2720 gas chromatograph, using a thermal conductivity detector and helium as the carrier gas. The stainless steel column was 1.83 m × 0.64 cm containing 10 % Carbowax 20M on Chromosorb W (80–100 mesh). The column temperature was 150 °C or 160 °C; the injection port was at 220 °C; the detector was kept at 225 °C. The unknown solutions were compared with standards prepared from the identified components.

*Isolation of 5 and 8.* After the usual work-up of an electrolysis reaction, starting with DMF, the ether solution was distilled at the water pump, and the fraction of b.p. 110–115 °C/15 mmHg was separated by preparative GLC into two fractions on a poly-*m*-phenyl ether column at 200 °C. Each of the fractions was rechromatographed on the same column at 180 °C.

The *vic*-compound, *5*, had the longer retention time, was obtained pure and was shown to be identical to chemically synthesized *5* by its NMR spectrum, its IR spectrum and its GLC retention time.

$^1$H NMR (60 MHz, $CDCl_3$): $\delta$ 1.20 (6 H, t, $CH_3$), 3.55 (4 H, q, $CH_2$), 4.80 (4 H, d, $NCH_2$), 8.35 (1 H, s, HCO).

The *gem*-compound, *7*, was obtained in admixture with *11*, and GLC analysis indicated that the sample contained 92 % *7* and 8 % *11*. Analysis of this mixture: C 50.98; H 9.87; N 8.67. Calc.: C 50.74; H 9.26; N 9.09. $^1$H NMR for *7*: $\delta$ 1.20 (6 H, t, $CH_3$), 2.85 (3 H, s, $NCH_3$), 3.55 (4 H, q, $CH_2$), 5.35 (1 H, s, CH), 8.35 (1 H, s, HCO).

*Isolation of 9.* The triethoxy compound, *9*, was isolated from a DMF electrolysis reaction mixture by preparative GLC on a Carbowax column at 180 °C, with the injection port and detector both at 225 °C. The retention time of *9* was intermediate between those for *11* and *5* and *7*.

$^1$H NMR (100 MHz, $CDCl_3$): $\delta$ 1.32 (9 H, t, $CH_3$), 2.70 (6 H, q, $CH_2$), 4.82 and 4.92 (2 H, s, $NCH_2$), 5.48 and 6.24 (1 H, s, NCH), 8.48 and 8.64 (1 H, s, HCO). MS (M 205): *m/e* 159 (16), 102 (100), 85 (21), 74 (51), 58 (49), 57 (22), 46 (53), 30 (26), 29 (13).

*Preparation of 5.* This was first prepared from formamide, sodium hydride and ethyl chloromethyl ether following the procedure reported for the preparation of *4*.[6] The product, obtained in this manner in poor yield, could not be purified by distillation and was isolated by preparative GLC using the same conditions shown above for *5*. Anal. $C_7H_{15}NO_3$: C, H, N.

The following is a more satisfactory preparative procedure. A solution of *N*-ethoxymethylformamide (21.1 g; 0.205 mol) in monoglyme (65 ml) was added dropwise over a period of 20 – 30 min to a stirred suspension of sodium hydride (5 g; 0.208 mol) in monoglyme (200 ml). The mixture was protected from carbon dioxide and moisture by a drying tube filled with sodium hydroxide and dehydrite. Hydrogen evolved smoothly, and by the end of the addition the reaction product resembled shaving cream. Stirring was continued for an additional 30 min. A solution of chloromethyl ethyl ether (20.3 g; 0.205 mol) in monoglyme (65 ml) was added dropwise to the stirred suspension over a period of 45 min. The reaction mixture was then left overnight. The suspension was filtered by suction to give a slightly turbid solution. The sodium chloride residue was washed with ether, and the ether washings were added to the above filtrate. The solvents were removed at the water pump. Distillation at b.p. 75 – 78 °C/1 – 1.2 mmHg gave *5* in 69 % yield.

*Preparation of* 11. Using the electrochemical method and apparatus previously described,[7] two separate solutions, each containing *N*-methylformamide (40.3 g; 0.682 mol) and $Et_4NBF_4$ (10.9 g; 0.054 mol) in ethanol (130 ml) were electrolyzed at constant currents of 4 A and 5 A, respectively. The total charge passed was 2 F $mol^{-1}$ of amide. The cell contents were combined and treated with a large volume of ether. After filtration of $Et_4NBF_4$ the solution was distilled at 80 mmHg through a Vigreux column from a 45 °C water bath to remove ether and ethanol. The residue was distilled at 0.16 mmHg, and after several early fractions, 58.5 g of *11* was obtained, b.p. 63 – 72 °C. Analysis by GLC indicated that this fraction was 97 % pure. The early fractions were redistilled to yield 15.8 g, b.p. 61 – 66 °C/0.3 mmHg. This fraction was only 74 % pure by GLC analysis. The total current yield was 48.8 %.

*Preparation of* N,N-*bis(pentamethylbenzyl)formamide*, 14. A solution of *5* (1.61 g; 0.01 mol) and pentamethylbenzene (2.97 g; 0.02 mol) in redistilled trifluoroacetic acid (10 ml) and dichloromethane (30 ml) was refluxed for 24 h. The reaction mixture was taken up in benzene (250 ml), and the benzene solution was extracted with water (2 × 200 ml), with saturated sodium bicarbonate solution and then again with water. The benzene solution was dried over magnesium sulfate, and the solvents were removed *in vacuo*, and the product was recrystallized from ethyl acetate to yield 2.6 g (71 %) of *14*, m.p. 179 – 180 °C. Anal. $C_{25}H_{35}NO$: N.

*Reaction of* 15 *with pentamethylbenzyl chloride*. To *N*-pentamethylbenzylformamide, *15* (2.09 g; 0.0102 mol), prepared as previously described,[9] in warm tetrahydrofuran (40 ml) was added sodium hydride (0.296 g; 0.0123 mol). A condenser with a drying tube was attached and the mixture was refluxed with magnetic stirring for 1.5 h. The resultant suspension was treated dropwise with stirring over a 20 min period with a solution of pentamethylbenzyl chloride[10] (2.43 g; 0.0124 mol) in tetrahydrofuran. Refluxing and stirring were continued for 16 h after which time the solvent was removed with a stream of air. The white solid residue was digested several times with portions of ethyl acetate totalling 250 ml. After each digestion the supernatant liquid was decanted and filtered. The combined filtrates were concentrated to a volume of 100 ml and cooled, yielding 2.2 g (58 %) of crude *14*, m.p. 171 – 174 °C. Recrystallization raised the melting point to 176 – 178 °C. This sample of *14* was undepressed in melting point on admixture with *14* prepared by the amidoalkylation procedure described above.

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