

## ANODIC OXIDATION OF N-METHYLFORMAMIDE AND N-METHYLACETAMIDE

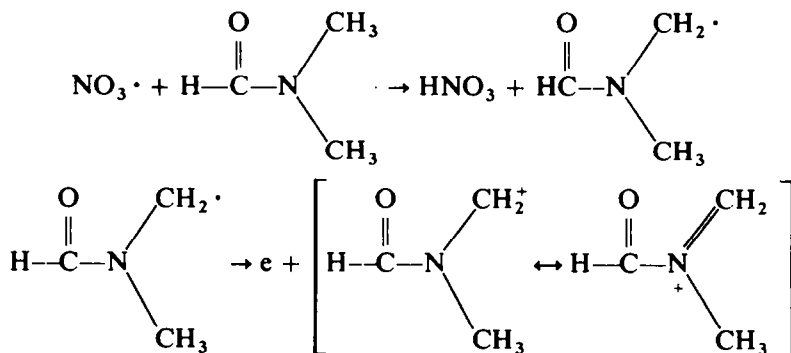
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(Received in the USA 10 April 1972; Received in the UK for publication 5 June 1972)

**Abstract**— The oxidation of N-methylalkylamides in alcohols was studied at platinum and carbon anodes using quaternary ammonium nitrates and fluoborates as supporting electrolytes. The most satisfactory conditions for the preparation of N-alkoxymethylalkylamides by this reaction involved the use of a platinum anode and a quaternary ammonium fluoborate. At a carbon anode, the major reaction is oxidation of the alcohol solvent to aldehyde, which is isolated as the acetal.

N-METHYL-N-ALKOXYMETHYLFORMAMIDES are conveniently prepared from N,N-dimethylformamide (DMF) by anodic oxidation.<sup>1,2</sup> The operation of two oxidation mechanisms has been demonstrated. In one, e.g., with a quaternary ammonium fluoborate as the supporting electrolyte where the coulombic yields approach 100%, the primary reaction is an electron transfer from the amide to give a cation-radical. In the other, the initiating reaction is an electron transfer from nitrate ion to give a nitrate radical, which then abstracts a hydrogen atom from DMF giving a new radical, which is oxidized anodically to a carbonium ion.



With a quaternary ammonium nitrate as the supporting electrolyte, both mechanisms have been shown to operate.

Since secondary amides are oxidized at significantly higher potentials than the corresponding tertiary amides,<sup>3</sup> it was of interest to determine if N-alkoxymethylalkylamides could be obtained similarly. Couch<sup>4</sup> has reported that the electrochemical oxidation of N-methylformamide (NMF) in the presence of 5–10% of 1 M sulfuric acid gives 2,6-diaza-4-oxa-1,7-heptanedione, while O'Donnell and Mann<sup>5</sup> reported that anodic oxidation of N-alkyl secondary amides in acetonitrile leads to dealkylation.

Several N-alkoxymethylalkylamides have been reported. Chwala<sup>6</sup> prepared

N-methoxymethylacetamide by the base catalyzed reaction of acetamide and formaldehyde followed by acid catalyzed etherification with MeOH. N-methoxymethylformamide was also prepared, in poor yield, by the same method, but the products were not adequately characterized. Linstead *et al.*<sup>7</sup> reported the preparation of N-methoxymethylacetamide by the electrolysis of acetylglycine in MeOH. This reaction can be interpreted as proceeding through the decarboxylation of an  $\alpha$ -substituted acetic acid followed by subsequent oxidation of the intermediate radical to form a carbonium ion:

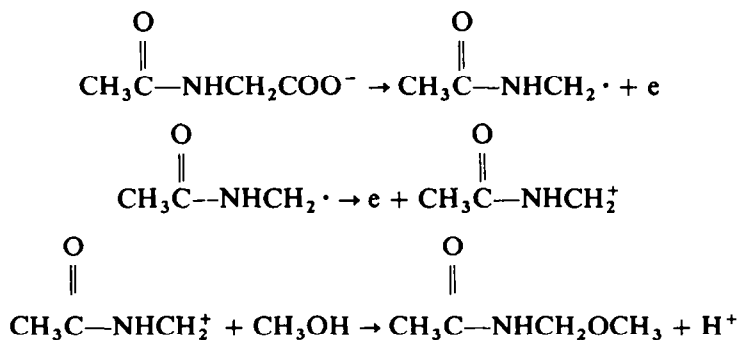


Table 1 summarizes the results of the present investigation, and Table 2 lists the properties of the products formed. The electrolyses were run at constant current,

TABLE 1. ANODIC OXIDATION OF N-METHYLAMIDES

Amide	Solvent	Anode	Supporting Electrolyte	Current (amp)	Charge Passed	Product <sup>b</sup>	Coulombic Yield (%)
NMF	MeOH	Pt	(Bu) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	3.0	0.432F	A	60.3 <sup>c</sup>
NMF	EtOH	Pt	(Et) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	3.0	0.698F	B	39.3
NMF	n-BuOH	Pt	(Bu) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	1.0	0.40 F	C	44.2
NMA <sup>a</sup>	MeOH	Pt	(Et) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	3.0	0.30 F	D	31.7
NMF	MeOH	C	(Bu) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	4.0	0.627F	A	trace
NMF	EtOH	C	(Et) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	3.0	0.707F	B	3.2 <sup>d</sup>
NMF	n-BuOH	C	(Bu) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	2.0	0.40 F	C	trace
NMA <sup>a</sup>	MeOH	C	(Et) <sub>4</sub> N <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	3.0	0.30 F	D	trace
NMF	MeOH	Pt	(Et) <sub>4</sub> N <sup>+</sup> NO <sub>3</sub> <sup>-</sup>	3.0	0.679F	A	4.5 <sup>d</sup>
NMF	MeOH	C	(Et) <sub>4</sub> N <sup>+</sup> NO <sub>3</sub> <sup>-</sup>	3.0	0.679F	B	1.4

<sup>a</sup> N-methylacetamide

<sup>b</sup> Refer to Table 2 for structure

<sup>c</sup> Average of 2 experiments

<sup>d</sup> Maximum yield

using either a quaternary ammonium fluoborate or a quaternary ammonium nitrate as the supporting electrolyte. The coulombic yields, based on the assumption that 2 F of charge are required to form a mole of product, were determined either from analyses of the reaction mixtures by VPC or by isolation of the pure products.

The results in Table 1 indicate that the most suitable conditions for the preparation

of N-alkoxymethylalkylamides are electrolysis at a platinum anode with a quaternary ammonium fluoborate as the supporting electrolyte. The use of quaternary ammonium nitrates results in only small amounts of product, and at a carbon anode very little of the desired reaction takes place.

TABLE 2. ELECTROLYSIS PRODUCTS

Compound	b.p.	RI	%N Calc.	Found
N-Methoxymethylformamide (A)	55-58°/0.1 mm	$n_D^{24} = 1.4417$	15.72	15.76
N-Ethoxymethylformamide (B)	56-57°/0.05 mm	$n_D^{25} = 1.4380$	13.58	13.59
N-Butoxymethylformamide (C)	69-75°/0.02 mm	$n_D^{25} = 1.4416$	10.68	10.45
N-Methoxymethylacetamide (D)	69-70°/0.21 mm	$n_D^{25} = 1.4392$	13.58	13.70

The acid catalyzed interchange of the alkoxy groups in the N-alkoxymethyl-N-methylalkylamide series is a rapid, preparatively useful reaction.<sup>8</sup> With the N-alkoxymethylalkylamides, the reaction is slow and unsatisfactory. For example, a solution of N-ethoxymethylformamide in MeOH, treated with a few drops of concentrated H<sub>2</sub>SO<sub>4</sub> shows, by VPC, a decreasing amount of N-ethoxymethylformamide and the gradual formation of a small amount of N-methoxymethylformamide, but even after long periods of time the reaction does not go to completion. If larger amounts of acid are added, both starting material and product are destroyed. In contrast, a solution of N-ethoxymethyl-N-methylformamide in MeOH underwent considerable exchange before the addition of acid and was completely and rapidly converted to N-methoxymethyl-N-methylformamide after addition of a small amount of acid.

The structure of the product obtained by anodic oxidation of N-methylacetamide in MeOH was based on the nitrogen analysis and the reaction with phthalimide to give N-phthalimidomethylacetamide, m.p. 219-221° (lit.<sup>7</sup> 184°). A mixed m.p. with an authentic sample prepared by the method of Buc<sup>9</sup> showed no depression.

A similar reaction between phthalimide and N-methoxymethylformamide gave a product, m.p. 167-169°, which had the correct nitrogen analysis for N-phthalimidomethylformamide. Further proof of the structure of the product from the oxidation of NMF in MeOH was obtained by applying the above cited reaction of Linstead *et al.*<sup>7</sup> to formylglycine. Electrolysis of N-formylglycine at a platinum anode in MeOH containing NaOMe gave a 30% coulombic yield of N-methoxymethylformamide, which was shown by VPC and IR spectra to be identical with the product from the anodic oxidation of NMF in MeOH.

The structure of the product obtained by electrolysis of NMF in EtOH was established by synthesis to be N-ethoxymethylformamide. The method of Parris<sup>10</sup> was adapted to the preparation of N-hydroxymethylformamide, and this was allowed to react with absolute EtOH in the presence of acid at room temperature. The product obtained was shown to be identical to the electrolysis product by VPC and by its RI.

The contrast in electrochemical behavior between DMF and NMF is striking. Preparative anodic oxidation of DMF is successful at both platinum and carbon anodes with either nitrate or fluoborate salts, while practical synthetic procedures

with NMF are limited to a platinum anode and fluoborate salts. At the carbon anode, the alcohols used as solvents are preferentially oxidized. When a mixture of NMF, tetrabutylammonium fluoborate and *n*-BuOH was oxidized at a carbon anode, only a trace of *N*-butoxymethylformamide could be detected by VPC. The major product isolated was the dibutylacetal of butyraldehyde, and the same product was obtained by oxidation of *n*-BuOH at a carbon anode in the absence of NMF. The structure of the acetal was confirmed by synthesis of an authentic sample from butyraldehyde and *n*-BuOH. The other alcohols used as solvents in this work could also be oxidized electrochemically at carbon to give acetals derived from oxidation of the alcohol. This reaction has been reported by Sundholm.<sup>11, 12</sup>

The failure to obtain *N*-alkoxymethylformamides when nitrates are used as the supporting electrolytes is not fully explained. The higher oxidation potential of NMF compared to DMF makes it highly probable that the hydrogen atom abstraction mechanism will predominate in this system. It is possible that the abstraction by nitrate radical is from the weaker N—H bond rather than from the C—H bond and that the radical species so formed does not lead to product.

#### EXPERIMENTAL

*Electrolyses.* The electrolysis cell and electrode assemblies are those previously described<sup>13</sup> for use in constant current procedures. The following two procedures, one at platinum and one at carbon are typical of those used.

*Electrolysis of NMF in butanol at a platinum anode.* A solution of NMF (11.8 g, 0.2 mole) and tetrabutylammonium fluoborate (16.5 g, 0.05 mole) in *n*-BuOH (150 ml) was electrolyzed with a constant current of 1.0 amp until 0.40 F of charge was passed. BuOH was removed and the residue stirred with fresh portions of ether until the fluoborate salt crystallized. The combined ether extracts were filtered, and the ether removed. The residue was distilled at 0.015 mm giving a main fraction of 15.6 g, b.p. 75–78°:  $n_D^{23} = 1.4412$ . Redistillation at 0.02 mm gave 11.6 g of *N*-butoxymethylformamide; b.p. 67–75°:  $n_D^{25} = 1.4412$ .

*Electrolysis of NMF in butanol at a carbon anode.* A solution of NMF (11.89 g, 0.2 mole) and tetrabutylammonium fluoborate (16.5 g, 0.05 mole) in redistilled *n*-BuOH (150 ml) was electrolyzed at a current of 2.0 amp until 0.40 F of charge was passed. BuOH was removed and the residue repeatedly stirred with fresh portions of ether until the salt had crystallized. The combined ether extracts were filtered and the ether removed by distillation. The residue, which contained only a trace of *N*-butoxymethylformamide, was distilled at 16 mm. The distillate separated into layers—a lower layer of recovered NMF and an upper product layer, which was separated. Distillation of product layer yielded 6.8 g of the dibutylacetal of butyraldehyde; b.p. 100–104°/13 mm, identical to an authentic sample prepared by a modification of the method of Adkins and Nissen.<sup>14</sup>

*Electrolysis of *n*-butanol at a carbon anode.* A solution of tetrabutylammonium fluoborate (16.5 g, 0.05 mole) in distilled *n*-BuOH (160 ml) was electrolyzed with a current of 1.5 amp until 0.446 F was passed. The *n*-BuOH was distilled at 15–20 mm. Ether was added to the residue, and the mixture stirred. The salt, which crystallized, was filtered, and the filtrate distilled at 15 mm, yielding a main fraction of 11.3 g of the dibutylacetal of butyraldehyde; b.p. 100–108°:  $n_D^{20} = 1.4162$ . An earlier fraction, 1.9 g, b.p. 91–100°,  $n_D^{20} = 1.4123$ , was also largely the acetal.

*Electrolysis of DMF in methanol at a carbon anode.* A solution of DMF (70.8 g, 0.97 mole) and tetraethylammonium fluoborate (10.85 g, 0.05 mole) in MeOH (75 ml) was electrolyzed at a current of 3.0 amp until 0.95 F of charge was passed. MeOH was removed and the residue stirred with ether; the solid filtered and the ether distilled. The residue distilled at 6 mm to give several fractions containing *N*-methoxymethyl-*N*-methylformamide, with the main fraction boiling at 61–68°. Analysis of the various fractions by VPC showed that a total of 41.6 g, 84.7% coulombic yield, of *N*-methoxymethyl-*N*-methylformamide had been formed.

*Electrolysis of *N*-formylglycine.* *N*-Formylglycine was prepared by the method of Tipsón and Pawson.<sup>15</sup> A suspension of *N*-formylglycine (20.6 g, 0.2 mole) in a solution obtained by reacting sodium (0.54 g,

0.0235 g at) with MeOH (160 ml) was electrolyzed at a platinum anode with a current of 2.0 amp until 0.609 F of charge was passed. During the electrolysis, the electrodes became badly pitted, and a large amount of black solid deposited. The mixture was filtered through sintered glass. Celite was added, and the mixture was again filtered through paper. The filtrate was stirred for one h with solid  $\text{NaHCO}_3$ , again filtered, and the filtrate distilled at water pump until a solid appeared. Ether was added. The solid was separated, and the solution distilled at 0.1 mm, yielding a main fraction of 8.1 g (30% coulombic yield) of N-methoxymethylformamide: b.p. 52–55°;  $n_D^{23} = 1.4415$ .

*Preparation of authentic N-methoxymethylacetamide.* The method of Parris<sup>10</sup> was used to prepare N-hydroxymethylacetamide, which was converted to N-methoxymethylacetamide by the procedure of Chwala:<sup>6</sup> b.p. 58–62° at 0.01 mm;  $n_D^{20} = 1.4375$ .

*N-Phthalimidomethylacetamide.* An equimolar mixture of N-methoxymethylacetamide and phthalimide was heated above the melting point for 5 min. The product was crystallized first from EtOH and then MeOH: m.p. 218–220°. The same product was obtained by the method of Buc:<sup>9</sup> m.p. 220–223°. A mixed m.p. with the two products showed no depression.

The same compound, m.p. 219–221°, was also obtained by heating the electrolysis product of N-methylacetamide and MeOH with phthalimide.

*N-Ethoxymethylformamide.* 40% KOH aq (2 ml) was added to a mixture of formamide (45 g, 1.0 mole) and paraformaldehyde (33 g, 1.1 mole). The solid dissolved, and the solution was left standing 30 min. After addition of EtOH (200 ml) and conc  $\text{H}_2\text{SO}_4$  (3 ml), the mixture was let stand for 6 h. The white solid which precipitated was filtered with suction, and anhydrous ether (20 ml) added to the filtrate. This solution was stirred with  $\text{NaHCO}_3$  and left standing overnight. After filtration at the water pump, the filtrate was distilled. A main cut of 19.4 g, b.p. 71–82°/0.01–0.10 mm, was obtained before the distillation was stopped due to accumulation of white solid in the condenser. The distillate was redistilled at 0.05 mm yielding 11 g of product: b.p. 54–71°;  $n_D^{20} = 1.4413$ .

*N-Phthalimidomethylformamide.* A mixture of phthalimide (8.7 g, 0.059 mole) and N-methoxymethylformamide (5.2 g, 0.059 mole) was melted together and heated five min. The crude product was fractionally crystallized from acetone. A pure head fraction was crystallized from chloroform-hexane to give 1.1 g of N-phthalimido-methylformamide: m.p. 167–169°. (Calc. for  $\text{C}_{10}\text{H}_7\text{N}_2\text{O}_3$ : N = 13.72. Found: N = 13.52%).

*Exchange between N-ethoxymethylformamide and methanol.* A solution of N-ethoxymethylformamide (1 ml) in MeOH (10 ml) was analyzed by VPC and showed only the peak due to the N-ethoxymethyl compound. After the successive addition of 6 drops of conc  $\text{H}_2\text{SO}_4$  over a one-hour period, VPC analysis of the solution indicated the presence in the solution of approximately an equimolar mixture of N-methoxymethylformamide and N-ethoxymethylformamide. An attempt to force the reaction to completion by the addition of more  $\text{H}_2\text{SO}_4$  resulted in the disappearance of the VPC peaks due to the above two compounds and the precipitation of ammonium sulfate.

*Exchange between N-ethoxymethyl-N-methylformamide and methanol.* A solution of N-ethoxymethyl-N-methylformamide (1 ml) in MeOH analyzed by VPC, immediately after mixing, indicated extensive conversion to the N-methoxymethyl compound. The addition of two drops of conc  $\text{H}_2\text{SO}_4$  drove the reaction rapidly to completion.

*Analysis by VPC.* VPC analyses were carried out with a Perkin-Elmer model 154B vapor fractometer using helium as carrier gas and a Perkin-Elmer large diameter Golay column (0.06 in.  $\times$  300 ft.) in which the stationary phase was Ucon polyglycol LB-550-X.

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