Anodic Oxidations. III. The Reaction Mechanism in the Electrochemical Acetoxylation and Alkoxylation of N,N-Dimethylamides

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Abstract: N-Alkoxymethyl-N-methylamides can be prepared, in good yield, by electrolyzing solutions of ammonium nitrate in an N,N-dimethylamide and an alcohol. Electrolysis of a solution of ammonium nitrate in dimethylformamide and acetic acid yields N-acetoxymethyl-N-methylformamide, and electrolysis of a solution of ammonium nitrate in dimethylformamide containing small amounts of water gives 2,6-diformyl-2,6-diaza-4-oxaheptane. These reactions involve the discharge of nitrate ion at the anode as the first step and the carbonium ion, $RCON(CH_3)CH_2^+ \longleftrightarrow RCON^+(CH_3){=}CH_2$, as the product-forming intermediate.

There is a substantial body of evidence indicating that the anodic acetoxylation of both N,N-dimethylamides and aromatic hydrocarbons involves the anodic oxidation of the substrate rather than acetate ion or acetic acid.[1-7] The essential evidence, that dimethylformamide and aromatic hydrocarbons can be acetoxylated electrochemically in acetate ion–acetic acid at anode potentials too low to permit the Kolbe reaction to occur, has been presented by Eberson.[8]

The formyloxylation of dimethylformamide is less clear-cut. The oxidation of formic acid occurs at a much lower potential than does the oxidation of acetic acid, and in the formate ion–formic acid system it is not possible to demonstrate incisively that dimethylformamide is oxidized at a potential lower than that required for the oxidation of either formate ion or formic acid.[5]

It is the purpose of the present report to show that even the acetoxylation of dimethylformamide can be effected under conditions which involve, as the first step, the anodic oxidation of an anion rather than the substrate, dimethylformamide. In addition, these studies have resulted in an efficient, practical electrochemical synthesis of N-alkoxymethyl-N-methylamides.

Results

The electrochemical alkoxylation of furan derivatives to 2,5-dialkoxy-2,5-dihydrofurans has been known since the pioneering work of Clauson-Kaas.[9] More recently, Belleau and Weinberg[10] have reported the electrochemical methoxylation of *p*-dimethoxybenzene to a 75% yield of 3,3,6,6-tetramethoxy-1,4-cyclohexadiene and of *m*-dimethoxybenzene to a 61% yield of 2,3,3,6,6-pentamethoxy-1,4-cyclohexadiene. With *o*-dimethoxybenzene a mixture of four methoxylated products resulted. Inoue, *et al.*,[11] have described the successful anodic methoxylation of a variety of substrates, *e.g.*, stilbene, diphenylmethane, tetralin, and styrene. These studies include examples of substitution reactions (replacement of hydrogen by methoxyl) as well as of additions to unsaturated systems.

Electrolysis of a methanol solution of sodium methoxide and dimethylformamide resulted in the formation of isolable quantities of N-methoxymethyl-N-methylformamide. Comparable results were obtained in the preparation of N-ethoxymethyl-N-methylformamide when an ethanol solution of sodium ethoxide and dimethylformamide was electrolyzed. Neither reaction, however, appeared to represent a completely satisfactory preparative procedure.

When the sodium alkoxides in the above reactions were replaced with ammonium nitrate, clean reactions giving the desired products in good yields resulted. The reaction appears to be general for N,N-dimethylamides, and the ether amides shown in Table I have been prepared by this procedure. The reported yields are based on the charge passed, with the assumption that formation of 1 mole of the ether amide requires 2 Faradays. N-Ethoxymethyl-N-methylbenzamide could not be obtained in pure form by distillation. The crude product, obtained in 54.4% yield by distillation, had bp 90–100° at 0.075 mm, and $n^{24.5}$D 1.5310, and was contaminated with N,N-dimethylbenzamide. The properties for this product, given in Table I, are for a sample purified by vpc.

Two of the compounds in Table I, N-methoxymethyl-N-methylformamide and N-ethoxymethyl-N-methylformamide, had been prepared previously by the reactions of N-formyloxymethyl-N-methylformamide with methanol and ethanol, respectively.[12] For comparison purposes, N-*n*-butoxymethyl-N-methylformamide has now also been prepared from N-formyloxymethyl-N-methylformamide and 1-butanol, and N-*n*-butoxymethyl-N-methylacetamide has been prepared from

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(1) L. Eberson, *Acta Chem. Scand.*, **17**, 2004 (1963).

(2) L. Eberson and K. Nyberg, *ibid.*, **18**, 1568 (1964).

(3) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.*, **86**, 2745 (1964).

(4) S. D. Ross, M. Finkelstein, and R. C. Petersen, *ibid.*, **86**, 4139 (1964).

(5) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, **31**, 128 (1966).

(6) M. Leung, J. Herz, and H. W. Salzberg, *ibid.*, **30**, 310 (1965).

(7) H. W. Salzberg and M. Leung, *ibid.*, **30**, 2873 (1965).

(8) L. Eberson and K. Nyberg, *J. Am. Chem. Soc.*, **88**, 1686 (1966). We are much indebted to Professor Eberson for sending us a copy of his manuscript before publication.

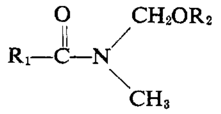
(9) N. Clauson-Kaas, F. Lunborg, and K. Glens, *Acta Chem. Scand.*, **6**, 531 (1952); N. Clauson-Kaas, *ibid.*, **6**, 569 (1952); N. Clauson-Kaas and Z. Tyle, *ibid.*, **6**, 667, 962 (1952).

(10) B. Belleau and N. L. Weinberg, *J. Am. Chem. Soc.*, **85**, 2525 (1963).

(11) T. Inoue, K. Koyama, T. Matsouka, and S. Tsutsumi, *Tetrahedron Letters*, **21**, 1409 (1963); T. Inoue, K. Koyama, and S. Tsutsumi, *Bull. Soc. Chem. Japan*, **37**, 1597 (1964); T. Inoue and S. Tsutsumi, *ibid.*, **38**, 661 (1965).

(12) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, **31**, 133 (1965).

Table I. N-Alkoxymethyl-N-methylamides

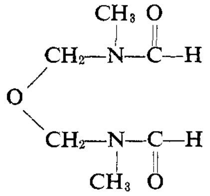


R_1	R_2	Bp, °C	Pressure, mm	nD	Yield, %	Calcd, %			Found, %		
						C	H	N	C	H	N
H	CH_3	72–75	15	1.4325 at 23.5°	52.0						
H	C_2H_5	69–71	8	1.4325 at 24.0°	66.8						
H	n-C_4H_9	61	0.01	1.4364 at 23.5°	81.6	57.90	10.41	9.65	57.80	9.98	9.70
									57.79	10.23	9.43
CH_3	n-C_4H_9	48–50	0.008	1.4396 at 23.5°	77.75	60.35	10.76	8.80	60.56	10.66	8.80
									60.27	10.70	8.55
C_6H_5	C_2H_5			1.5179 at 24.0°		68.37	7.82	7.25	68.18	7.49	7.22

N-acetoxymethyl-N-methylacetamide and 1-butanol. In every case the product obtained from the electrochemical reaction was identical with the product prepared by purely chemical means.

Ammonium nitrate may also be used in place of sodium acetate in the electrochemical preparation of N-acetoxymethyl-N-methylformamide.[5] As will be shown later, although the same product is obtained with ammonium nitrate, it appears to arise from a different and more favorable reaction path and is obtained in much better yield. The use of ammonium nitrate cannot be extended to the reactions in formic acid, since the acid is rapidly decomposed by the nitrate at room temperature.

Electrolysis of a solution of ammonium nitrate in dimethylformamide containing 3.2% water results in the formation of 2,6-diformyl-2,6-diaza-4-oxaheptane, I. This product had been obtained previously as a by-product in the electrochemical preparation of N-formyloxymethyl-N-methylformamide.[3] It has also been obtained in the electrolysis of dimethylformamide containing 5–10% of 1 M sulfuric acid,[13] and can be prepared chemically by treating N-methylformamide with paraformaldehyde in the presence of hydrochloric acid.[14]



I

Discussion

The electrochemical reactions which have been described represent a convenient and apparently general procedure for the conversion of N,N-dimethylamides to N-alkoxymethyl-N-methylamides. To understand the mechanism of these reactions it is essential to know which chemical species is being oxidized at the anode. The pertinent current–voltage curves have, therefore, been investigated both by a method previously described which used a mercury pool reference electrode[5] and also using a silver–silver chloride reference electrode. For the latter measurements the solutions contained lithium chloride in addition to the nitrate salt.

The results for the ethanol–ammonium nitrate system are shown in Figures 1 and 2 and the results for the acetic acid–ammonium nitrate system are given in Figures 3 and 4. As may be seen from the figures, the addition of dimethylformamide does not change the current–voltage curve in either system. Thus the species being oxidized in these systems is either the solvent or nitrate ion. Since it has already been demonstrated that dimethylformamide is oxidized at a lower potential than acetic acid,[5,8] it follows that in the acetic acid–ammonium nitrate system it is nitrate ion which is being discharged.

This conclusion has been confirmed by measuring the rate of gas evolution in a solution containing acetic acid, ammonium nitrate, and dimethylformamide. The procedure used was the one previously described,[4] and the result is unequivocal. There is no gas generated at the anode. The only gas formed was hydrogen, obtained at the cathode in exactly the theoretical quanitity, *i.e.*, 1 mole of hydrogen for every 2 Faradays of charge passed. Under the same experimental conditions in a system containing potassium acetate in place of ammonium nitrate, 60% or more of the normal Kolbe anodic reaction takes place as evidenced by the amounts of carbon dioxide and ethane generated.[5] This is the observed result under the experimental conditions used in spite of the fact that dimethylformamide is oxidized at a lower potential than acetic acid. It follows with certainty that in the presence of ammonium nitrate, where neither ethane nor carbon dioxide is formed, that only nitrate ion is discharged at the anode. That the addition of potassium acetate to the solution containing acetic acid, dimethylformamide, and ammonium nitrate alters neither the rate of gas formation nor the gas composition is further support for this conclusion.

A comparable confirmatory experiment is not possible in the alcohol–ammonium nitrate system. Nevertheless, it is reasonable to conclude that in this system, too, it is nitrate ion that is discharged, since in this acidic solution no significant concentration of alkoxide is present.

In view of the foregoing, the mechanisms for these reactions must involve the discharge of nitrate ion at the anode in the first step. As shown in eq 1–5 below, this affords a pathway for formation of the carbonium ion

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(13) D. E. Couch, *Electrochim. Acta*, **9**, 327 (1964).

(14) J. H. Robson and J. Reinhart, *J. Am. Chem. Soc.*, **77**, 2453 (1955).

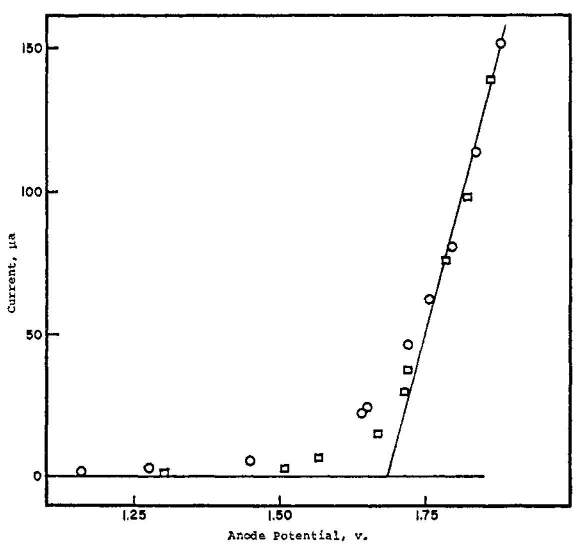


Figure 1. Plot of current *vs.* anode potential (relative to Hg pool) for electrolysis of solutions containing 0.010 mole of NH_4NO_3 in 50.0 ml of ethanol: ○, without dimethylformamide; □, with 0.5 ml of dimethylformamide added.

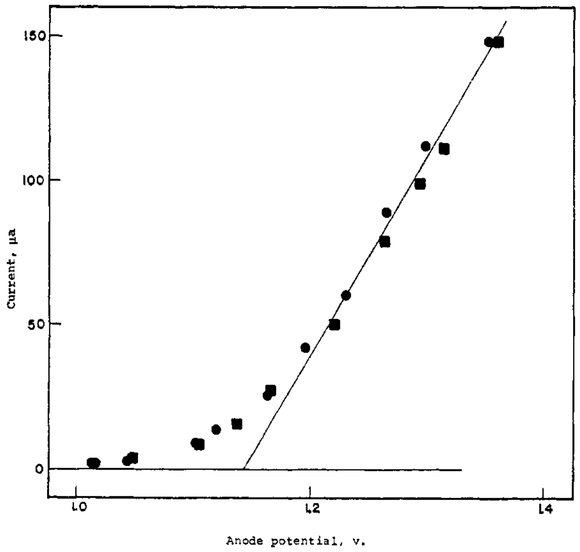
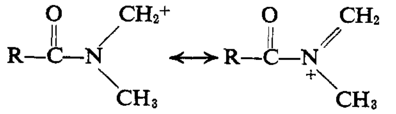


Figure 2. Plot of current *vs.* anode potential (relative to Ag–AgCl) for electrolysis of solutions containing 0.010 mole of NH_4NO_3 and 0.010 mole of LiCl in 50.0 ml of ethanol: ●, without dimethylformamide; ■, with 0.5 ml of dimethylformamide added.

II, regardless of whether the discharge of nitrate ion

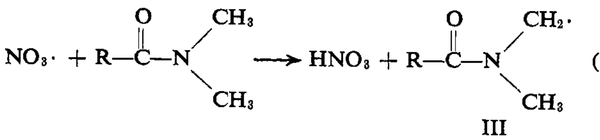


$$R-\overset{\overset{\displaystyle O}{\|}}{C}-N\begin{matrix}CH_2^+\\ \\ CH_3\end{matrix} \longleftrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{+}{N}\begin{matrix}{=}CH_2\\ \\ CH_3\end{matrix}$$

II

involves a one-electron or a two-electron transfer to the anode.

$$NO_3^- \longrightarrow e + NO_3\cdot \quad (1)$$



$$NO_3\cdot + R-\overset{\overset{\displaystyle O}{\|}}{C}-N\begin{matrix}CH_3\\ \\ CH_3\end{matrix} \longrightarrow HNO_3 + R-\overset{\overset{\displaystyle O}{\|}}{C}-N\begin{matrix}CH_2\cdot\\ \\ CH_3\end{matrix} \quad (2)$$

III

$$III \longrightarrow e + II \quad (3)$$

$$NO_3^- \longrightarrow 2e + NO_3^+ \quad (4)$$

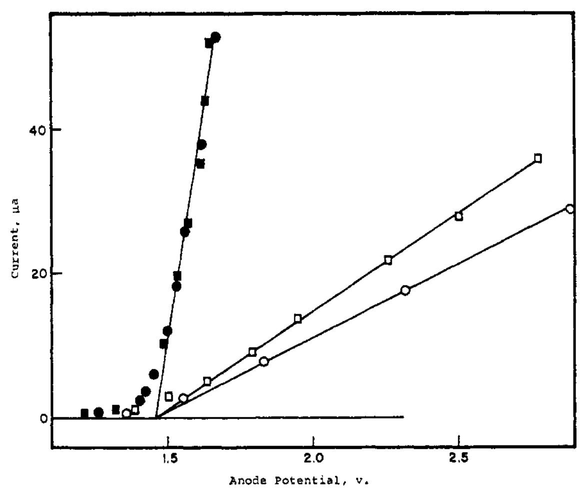


Figure 3. Plot of current *vs.* anode potential (relative to Hg pool) for electrolysis of solutions containing nitrate salts in 50.0 ml of glacial acetic acid: ○, saturated NH_4NO_3; □, NH_4NO_3 with 0.5 ml of dimethylformamide added (some of the sparingly soluble NH_4NO_3 had precipitated from solution, and on addition of DMF it redissolved, hence the change in slope corresponding to a change in conductivity); ●, 0.010 mole of $(CH_3)_4NNO_3$; ■, of $(CH_3)_4NNO_3$; with 0.5 ml of dimethylformamide added.

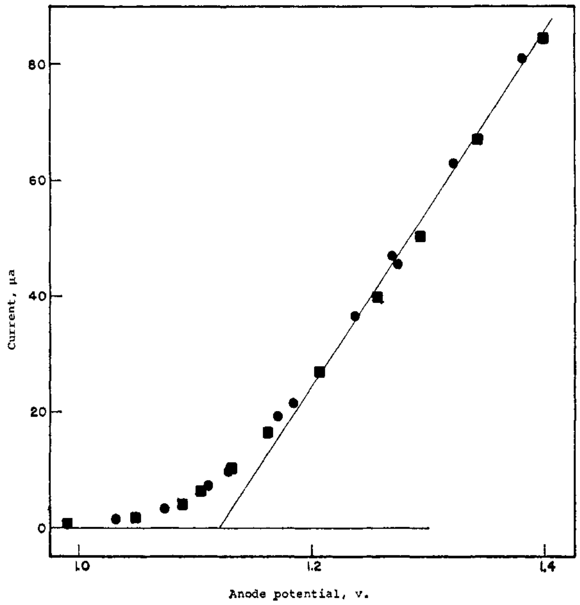
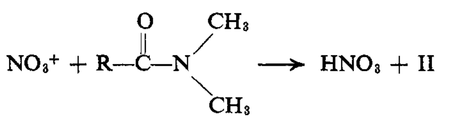
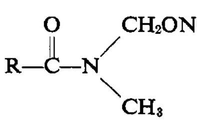


Figure 4. Plot of current *vs.* anode potential (relative to Ag–AgCl) for electrolysis of solutions containing 0.010 mole of $(CH_3)_4NNO_3$ and 0.010 mole of LiCl in 50.0 ml of ethanol: ●, without dimethylformamide; ■, with 0.5 ml of dimethylformamide added.



$$NO_3^+ + R-\overset{\overset{\displaystyle O}{\|}}{C}-N\begin{matrix}CH_3\\ \\ CH_3\end{matrix} \longrightarrow HNO_3 + II \quad (5)$$

A possible variation of these mechanisms might involve the formation of the nitrate ester, IV, as an intermediate. This ester could arise from reaction of



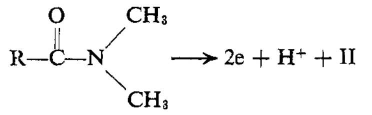
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-N\begin{matrix}CH_2ONO_2\\ \\ CH_3\end{matrix}$$

IV

III with $NO_3\cdot$ or from reaction of II with NO_3^-. The essential product-forming intermediate would, nevertheless, be II, generated from IV by an AAL1 mechanism[12] and reacting with either an alcohol or acetic acid to give the observed final products.

The formation of 2,6-diformyl-2,6-diaza-4-oxaheptane (I) in the electrolysis of dimethylformamide containing ammonium nitrate and water involves a similar reaction sequence. The carbonium ion II is generated; reaction with water gives N-hydroxymethyl-N-methylformamide, which reacts with a second molecule of II to give the final product.

The present results do not permit a decision as to whether the initial attack on the amide involves a hydrogen atom abstraction or a hydride ion abstraction. They do, however, demonstrate that nitrate ion is discharged at the electrode in the first step and point with some force to the carbonium ion, II, as the essential product-forming intermediate. Most important, they demonstrate that oxidation of the amide according to eq 6 is not the only electrochemical route


(6)

whereby II may be generated.[5,8]

Experimental Section

Rates of Gas Production and Gas Analysis. The electrolysis cell and the apparatus and methods used to collect and analyze the gases formed have been described previously.[4,15] The reaction cell was a water-jacketed cylinder of slightly more than 60-ml capacity, maintained at constant temperature with water circulated from a thermostat. The two platinum electrodes, each 1 cm^2 in area and at a separation of 0.6 cm, were inserted into the center of the cell through a ground-glass joint at the top. The rate of gas production was determined with a solution of ammonium nitrate (3.0 g, 0.0375 mole) in dimethylformamide (15 ml) and glacial acetic acid (30 ml). The electrolysis current was maintained constant at 0.40 amp. The current density in this measurement is approximately twice that used in the preparative electrolyses. The effect due to adding potassium acetate was determined by adding 3.25 g of potassium acetate to the above system.

Current-Voltage Curves. The apparatus and technique used to determine the current-voltage curves shown in Figures 1 and 3 were identical with those used previously to determine current-voltage curves during the electrolysis of formic and acetic acids both with and without added dimethylformamide.[5] Some of the sparingly soluble ammonium nitrate precipitated from the acetic acid solution prior to the current-voltage measurements and then redissolved when the dimethylformamide was added. The resultant change in conductivity is responsible for the observed differences in slope with and without dimethylformamide. This difficulty was obviated by using the more soluble tetramethylammonium nitrate as the source of nitrate ion. With this salt identical current-voltage curves and identical slopes were observed with and without dimethylformamide.

The measurements with the silver-silver chloride reference electrode were made in a stoppered 100-ml beaker fitted with a platinum wire anode, 0.035 cm in diameter, sealed into glass with a 0.217-cm length exposed to the solution, a platinum foil working electrolysis cathode and a wire silver-silver chloride reference electrode. Nitrogen was bubbled through the cell before and during the electrolysis, entering the solution just above the electrodes. The measuring procedure and equipment was the same as that used with the mercury pool reference electrode.

Preparation of the N-Alkoxymethyl-N-methylamides. The electrolysis cell consisted of a water-jacketed, 200-ml beaker fitted with a magnetic stirring bar, a thermometer, and a Teflon cover to which were attached two platinum electrodes, 0.025 cm thick, 2.5 cm wide, immersed to a depth of 7 cm and at a separation of 2 cm. The current was maintained at the highest value consistent with an applied voltage lower than 50 v and a reaction temperature below 60°, but it was not permitted to exceed 4 amp.

The description of the preparation of N-*n*-butoxymethyl-N-methylformamide, which follows, is representative. A solution of ammonium nitrate (8.0 g, 0.1 mole) in dimethylformamide (75 ml, 70.8 g, 0.97 mole) and 1-butanol (75 ml, 60.7 g, 0.81 mole) was electrolyzed until 1.26 Faradays of charge was passed through the solution. The current was 3 amp during most of the reaction but was decreased to 1 amp near the close of the electrolysis. Additional 1-butanol (20 ml) was added during the course of the electrolysis. The excess butanol was removed with the water pump, and ether was added. The precipitated salt was filtered, and the ether was removed. The residue was fractionated at 0.04 mm and yielded 74.6 g of N-*n*-butoxymethyl-N-methylformamide, bp 62–64°, $n^{23}\text{D}$ 1.4365. The amount of dimethylformamide converted to product was 53%. The yield based on the charge passed was 81.6%. A sample redistilled for analysis had bp 61° (0.01 mm) and $n^{23.5}\text{D}$ 1.4364.

The same product was obtained in 74% yield by treating N-formyloxymethyl-N-methylformamide with 1-butanol in the presence of a catalytic quantity of hydrochloric acid. The detailed procedure for this type of reaction has been described.[15]

N-Acetoxymethyl-N-methylformamide. A solution of ammonium nitrate (8 g, 0.1 mole) in dimethylformamide (50 ml, 0.65 mole) and acetic acid (100 ml) was electrolyzed at 3 amp until 0.653 Faraday of charge had passed through the solution. The reaction mixture was distilled at the water pump from a water bath maintained at or below 80° until no further distillate was obtained. Ether was added to the semisolid residue, and the ether solution was separated by filtration. The residue was shaken four more times with ether, and the combined filtered ether solutions were refiltered. The ether was removed by distillation through a Vigreux column, and the residue (42.5 g) was distilled at 0.06–0.10 mm. The yield was 26.7 g, bp 55–63°, $n^{25}\text{D}$ 1.4391. The yield based on the charge passed is 62.6%. Redistillation at 0.02 mm gave 23.0 g (53.9%) of product, bp 51–53°, $n^{24}\text{D}$ 1.4417. The infrared spectrum of this sample was identical with that of an authentic sample.

2,6-Diformyl-2,6-diaza-4-oxaheptane. A solution of ammonium nitrate (8.0 g, 0.1 mole) in dimethylformamide (150 ml) and water (5 ml) was electrolyzed at 4 amp until 1.19 Faradays of charge had passed through the solution. The excess water and dimethylformamide were removed with the water pump. The residue (47 g) was taken up in chloroform (500 ml) and extracted with two 25-ml portions of water. The chloroform solution was dried over magnesium sulfate, the chloroform was removed, and the residue was crystallized from ethyl acetate-ether, yielding 24.0 g of 2,6-diformyl-2,6-diaza-4-oxaheptane, mp 63–64°. If product formation involves the transfer of four electrons to the anode, the yield, based on the charge passed, is 50%.

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[15] R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961).