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Oxidation of Hydroxylamine Derivatives. I. Anodic Oxidation of Hydroxamic Acids

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The anodic oxidation of hydroxamic acids in acetonitrile were studied. These hydroxamic acids generally showed two or three waves at a glassy-carbon electrode and the E_p values were larger than those of the corresponding hydroxylamines.

On oxidation, O-alkylated hydroxamic acids consumed one electrone per molecule and other hydroxamic acids consumed two. Aceto- and benzohydroxamic acids gave the corresponding carboxylic acids and nitrous oxide. N-Substituted hydroxamic acids gave the corresponding nitroso compounds and carboxylic acids. O-Alkylated hydroxamic acids underwent intramolecular rearrangement of acyl and O-alkyl group to give esters, acids and alcohol. In the presence of added amines, acyl groups were recovered as amides.

From these results we proposed plausible chemical processes for the anodic oxidation of hydroxamic acids.

Keywords——anodic oxidation; hydroxamic acids; oxidative acylation; intramolecular acyl, O-alkyl rearrangement; glassy-carbon electrode

Hydroxamic acids, the acyl derivatives of hydroxylamine, N-hydroxycarbamates and N-hydroxyureas have been suggested to be metabolized to variety of oxidation products *in vivo*,[2] probably through acylation, alkoxycarbonylation and carbamoylations. Oxidation of hydroxamic acids with various chemicals has been shown to yield acylated products, but the nature of acylation species has not been established.[3]

By the electrochemical method using glassy-carbon electrode, we have clarified some of the oxidation intermediates and their reaction processes in the studies on several hydroxylamine derivatives.[4] As a continuation we examined the mechanism of electrochemical oxidation of hydroxamic acids.

Results

Cyclic Voltammetry

Results on the voltammetric behaviors of hydroxamic acids at a stationary glassy-carbon electrode in acetonitrile are summarized in Table I.[5]

Two or three irreversible waves were generally observed at a scanning rate of 0.2—0.05 V sec^{-1}. The second waves of N-methyl- and N-phenylacetohydroxamic acids were found to coincide with the oxidation waves of nitrosomethane and nitrosobenzene, respectively. The second waves of other four hydroxamic acids, however, appeared to be due to unstable intermediates because they were not detectable after exhaustive electrolyses at the first potential.

The hydroxamic acids are in general less susceptible to electrochemical oxidation than the corresponding hydroxylamines.[4] Attachment of a phenyl or a methyl group to the

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[1] Location: *133-1, Yamada-Kami, Suita-shi, Osaka.*

[2] *a*) B.S. Kathryn, A. Lossen, and J. Bernstein, *J. Med. Chem.*, **6**, 201 (1963); *b*) A.W. Pound, *Pathology*, **1**, 27 (1969).

[3] *a*) B. Sklartz and A.F.Al-Sayyab, *J. Chem. Soc.*, **1964**, 1318; *b*) A.R. Forester, M.M. Ogilvy, and R.Y. Thomson, *J. Chem. Soc.* (*C*), **1970**, 1081; *c*) T.R. Oliver and W.A. Waters, *J. Chem. Soc.* (*B*), **1971**, 677.

[4] *a*) H. Sayo, S. Ozaki, and M. Masui, *Chem. Pharm. Bull.* (Tokyo), **21**, 1988 (1973); *b*) *Idem*, *ibid.*, **23**, 1702 (1975).

[5] R.E. Plapinger, *J. Org. Chem.*, **24**, 802 (1959).

Table I. Cyclic Voltammetric Data on Hydroxamic Acids in Acetonitricle at 25°

Compd.[a]	E_p[b]		
		pyridine[c]	methylamine[c]
$C_6H_5CO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OH$	1.35	0.80	0.30
	1.65	1.20	0.85
	2.20	1.80	1.25
$MeCO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OH$	1.65	1.05	0.45
	2.10	1.80	0.80
	2.75		1.80
$C_6H_5CO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OMe$	1.60	0.95	0.50
	2.10	1.65	1.25
	2.75		1.60
$MeCO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OMe$	1.95	1.60	0.90
	2.15		1.50
			1.95
$MeCO\text{-}\underset{C_6H_5}{\underset{\vert}{N}}\text{-}OH$	1.15	0.70	0.35
	1.85	1.10	0.80
		1.85	1.85
$MeCO\text{-}\underset{Me}{\underset{\vert}{N}}\text{-}OH$	1.35	0.90	0.60
	1.60	1.35	1.35
		1.60	1.60

a) The structure of oxo form, $RCO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OH$ is the predominant species in solutions.[5]

b) volts *vs.* SCE

c) The mole ratio of (the added amine)/(hydroxamic acid) was about four.

Table II. Oxidation Products from Hydroxamic Acids

Compd.	$E_{app.}$[a]	n[b]	Amines added	Products	Yield (%)[c]
$C_6H_5CO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OH$	1.35	2.0		C_6H_5COOH	100
				N_2O	[d]
	0.40	1.9	-NH_2	C_6O_5CONH-	24
				C_6H_5COOH	[e]
	0.40	2.2	$MeNH_2$[f]	$C_6H_5CONHMe$	59
				C_6H_5COOH	4
$MeCO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OH$	1.60	2.0		$MeCOOH$	100
				N_2O	[d]
	0.60	2.1	$MeNH_2$[f,g]	$MeCOOH$	17,[f] 21[g]
				$MeCONHMe$	50[f] 75[g]
$C_6H_5CO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OMe$	1.60	1.0		C_6H_5COOMe	48
				C_6H_5COOH	26
				$MeOH$	42
$MeCO\text{-}\underset{H}{\underset{\vert}{N}}\text{-}OMe$	1.95	1.2		$MeCOOMe$	25
				$MeCOOH$	73
				$MeOH$	63
$MeCO\text{-}\underset{C_6H_5}{\underset{\vert}{N}}\text{-}OH$	1.20	1.9		$MeCOOH$	101
				$C_6H_5N{=}O$	94
$MeCO\text{-}\underset{Me}{\underset{\vert}{N}}\text{-}OH$	1.35	1.8		$MeCOOH$	63
				$MeN{=}O$	20
				$MeOH$	16
				$MeCON(Me)OH$	31
	0.60	3.1	$MeNH_2$[g]	$MeCOOH$	22
				$MeCONHMe$	58
				$MeN{=}O$	trace
				$HCHO$	94

a) applied potential in volts *vs.* SCE

b) the number of coulombs passed per mole of the substrate

c) mole per cent of starting hydroxamic acid

d) The quantitative analysis of nitrous oxide was not performed.

e) Benzoic acid, in the form of -$\overset{+}{N}H_3C_6H_5COO^-$ was not dissolved in acetonitrile and adsorbed on the carbon electrode and cell wall.

f) 40% methanolic solution

g) 40% aqueous solution

nitrogen atom shifted the first peak to negative potential, whereas O-methylation shifted it to positive potential. The results also showed that hydroxamic acids with a benzoyl group were more easily oxidized than those with an acetyl group and that the potential of the first peak, E_p, of those with an N-phenyl group were less than the E_p of those with an N-methyl group.

In the presence of excess bases, the hydroxamic acids showed one or two extra oxidation peaks at a much lower potential than that of the first peak. The potential of the extra peak decreased with increase in the basicity of the added amine. The first peak and the second peak of N-methyl- and N-phenylacetohydroxamic acids remained at nearly the same potential. The height of the first peak was found to decrease somewhat, whereas that of the second peak remained unchanged. The first peak of other hydroxamic acids except for O-methylacetohydroxamic acid also remained whereas the second peak of these hydroxamic acids were merged in background. Addition of excess water did not affect the cyclic voltammograms significantly.

Controlled Potential Electrolysis and Analysis of Products

The results obtained on controlled potential electrolysis of various hydroxamic acids are summarized in Table II.

Benzo- and Acetohydroxamic Acids——Benzo- and acetohydroxamic acids showed n values of 2.0 and yielded quantitative amounts of benzoic acid and acetic acid, respectively, with considerable nitrous oxide. No other products containing nitrogen, such as nitric acid or nitrous acid were detected. In the presence of aqueous amines, benzo- and acetohydroxamic acids yielded benzamide and acetamide, respectively. Using methanolic amine or undiluted amine instead of aqueous amine, the yield of N-methylacetamide increased slightly whereas that of acetic acid decreased.

O-Methylated Hydroxamic Acids——Table II shows that on coulometric electrolysis, the two hydroxamic acids showed n value of nearly 1. The acyl group was recovered nearly quantitatively as the corresponding carboxylic acids and methyl esters, and methyl group was recovered as methanol and methyl esters. No product containing nitrogen could be detected.

N-Phenyl- and N-Methylacetohydroxamic Acids——N-Phenyl- and N-methylacetohydroxamic acids showed n values of nearly 2, but their behaviors on coulometric electrolysis were fairly different; at the end of electrolysis of N-methylacetohydroxamic acid the current remained at a constant low level, whereas on electrolysis of the N-phenyl derivatives the current approached nearly zero exponentially.

Oxidation of N-phenylacetohydroxamic acid yielded acetic acid and nitrosobenzene quantitatively, but oxidation of N-methylacetohydroxamic acid yielded smaller amounts of acetic acid, nitrosomethane and much of the starting material remained unchanged. These results imply that further oxidation of nitrosomethane competed with oxidation of the starting material probably because the potential applied was close to that of nitrosomethane. (The E_p of nitrosomethane is 1.60 V *vs.* saturated calomel electrode (SCE)).

N-Methylacetohydroxamic acid was subjected to electrolysis at 0.60 V in the presence of excess methylamine (Table I). (The peak potential of methylamine itself is above 1.5 V *vs.* SCE in acetonitrile). Under these conditions, the n value approached 3, and the acetyl group was recovered as acetic acid and acetamide. Unexpectedly only trace of nitrosomethane was formed and the methyl group was recovered as formaldehyde.

Discussion

Hydroxamic acids, the acetyl derivatives of hydroxylamine, are reported to have the unexpected high acidity,[6] although most hydroxylamines are weak bases.

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[6] O. Exner and W. Simon, *Collection Czech. Chem. Commun.*, **30**, 4078 (1965).

On cyclic voltammetry, hydroxamic acids were found to be less susceptible to electrochemical oxidation than the corresponding hydroxylamines.[4] The peak potentials of a series of hydroxamic acids showed a similar trend to those of a series of hydroxylamines.[4] Among hydroxamic acids with a substituent of methyl group, the E_p values of the first peak decreased in the order: MeCONHOMe (1.90 V)>MeCONHOH (1.60 V)>MeCON(OH)Me (1.35 V), while their acidity is reported to decrease in the order: $R_1CONHOH > R_1CONHOR_2 > R_1CON(OH)R_2$.[6]

A similar disorder of p*K*a values and E_p values was observed among hydroxylamines with bulky substituent *t*-butyl group.[4]

The effects of substituents on the peak potential of hydroxamic acids described above suggest that the susceptibility of the compounds to electrochemical oxidation depends both on their acidity (or basicity), that is, the electron density and the steric environment of the atom from which the first electron is removed. The differences between the effects of a phenyl group and methyl group, and of a benzoyl group and acetyl group on the potential suggest that the stabilities of the cation radicals generated on removal of one electron also have strong effects on the oxidation potential.

The new oxidation peaks appearing on addition of excess amine seem to be due to oxidation of partially ionized hydroxamic acids, probably being assisted by the general base-type action of the added amine.[7] These new oxidation waves become less anodic with increase in the basicity of the added amine, because the degree of separation of the proton from the acid, that is, the electron density of the hetero atom depends on the strength of the added base.

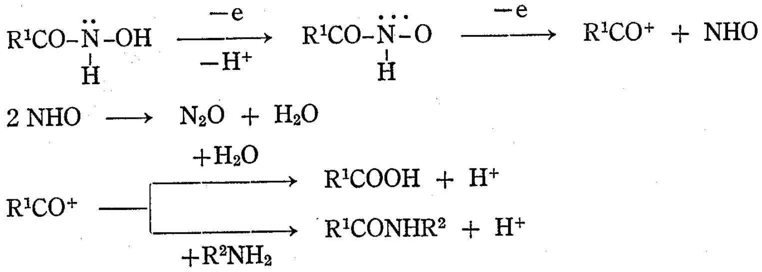
Controlled potential electrolysis and analysis of product showed that all the hydroxamic acids were oxidized completely at the primary oxidation potential without being inactivated through protonation except N-methylacetohydroxamic acid, as observed on oxidation of hydroxylamines.[4]

Possible reaction schemes for anodic oxidation of the hydroxamic acids were formulated on the basis of the oxidation products and the coulometric *n* values, and are described below.

Aceto- and Benzohydroxamic Acids

The *n* values of 2, the quantitative formation of acetic or benzoic acids, and formation of considerable amount of nitrous oxide suggest that a presumed intermediate, "an acyl nitroxyl radical," was oxidized further to an acyl cation and a nitroxyl radical.[8] Pairs of nitroxyl radicals probably couple giving nitrous oxide and water,[8] whereas the acyl cation reacts with water and added amines to give an acid and amides, respectively. The acyl cation should react faster with amines than with water, because the amide/acid ratio produced is over two, even on electrolysis in acetonitrile in which the concentration of water and methylamine are about 170 mM and 60 mM, respectively. However, the starting material was scarcely acylated.

The following reaction schemes seem most probable.



$$R^1CO\text{-}\underset{H}{\ddot{N}}\text{-}OH \xrightarrow[-H^+]{-e} R^1CO\text{-}\underset{H}{\dot{\ddot{N}}}\text{-}O \xrightarrow{-e} R^1CO^+ + NHO$$

$$2\,NHO \longrightarrow N_2O + H_2O$$

$$R^1CO^+ \begin{cases} \xrightarrow{+H_2O} R^1COOH + H^+ \\ \xrightarrow[+R^2NH_2]{} R^1CONHR^2 + H^+ \end{cases}$$

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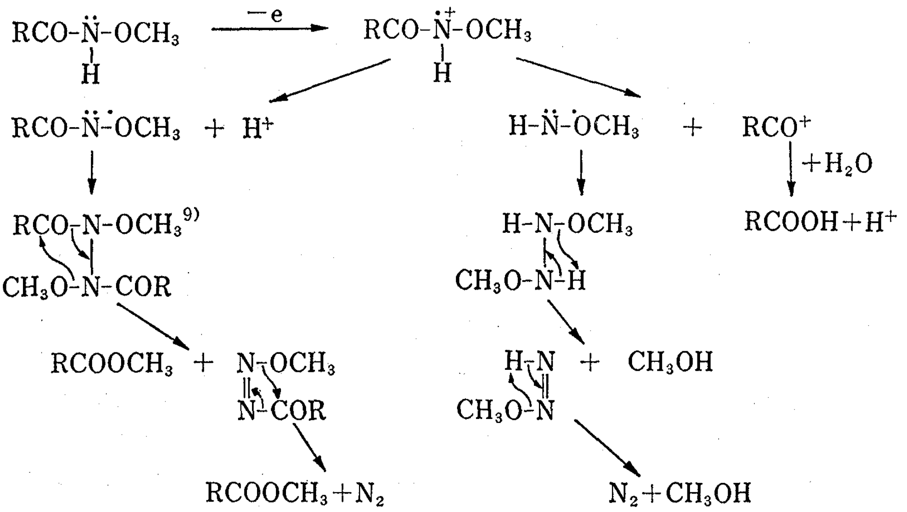
7) S. Ikenoya, M. Masui, H. Ohmori, and H. Sayo, *J. Chem. Soc. Perkin II*, **1974**, 541.

8) V.K. Jindal, M.C. Agrawal, and S.P. Mushran, *J. Chem. Soc.* (*A*), **1970**, 2060.

O-Methylated Hydroxamic Acids

The coulometric n value of 1 suggests that an intermediate is not oxidized further but that products are formed by some further chemical reactions. It seems likely that the intermediate formed by deprotonation and, or deacylation undergoes a coupling reaction and that this coupled intermediate yields the methylester of benzoic acid or acetic acid, methanol and probably nitrogen gas *via* intramolecular transformation of acyl and methoxy groups as follows.



If this is the reaction sequence, the yields of carboxylic acids and methanol should be nearly the same. The yield of benzoic acid was lower than that of methanol on electrolysis of O-methylbenzohydroxamic acid. This was probably because the method used for analysis of benzoic acid was unsatisfactory, as described in the experimental section. On oxidation of O-methylacetohydroxamic acid, the acetyl group seems to be the most easily cleaved from the cation radical, whereas on oxidation of O-methylbenzohydroxamic acid, deprotonation and debenzoylation seem to occur nearly equal extents.

N-Methyl- and N-Phenylacetohydroxamic Acids

N-Phenylacetohydroxamic acid seems to be oxidized to an acetyl cation and nitrosobenzene through a two-electron process, like that suggested to occur oxidations of aceto- and benzohydroxamic acids.

Controlled potential electrolysis of N-methylacetohydroxamic acid showed the intermediate radical was subject to two competitive processes, *i.e.* oxidation and probably disproportionation. On oxidation at the potential of 1.35 V, the intermediate radical and a part of the nitrosomethane produced should be oxidized yielding methanol, while at a lower potential of 0.60 V, intermediate radical should tend to undergo a disproportionation reaction to form the starting acid and a nitrone, N-acetylmethyleneamine N-oxide. The generated starting acid should be oxidized repeatedly by the same process, and the acetohydroxamic acid produced from the hydrolysis of the nitrone should be further oxidized, as the E_p of acetohydroxamic acid is 0.45 V in the presence of excess methylamine. When the reaction proceeds by route A to produce the nitroso derivative, n value is 2; while by route B and all of the nitrone produced could be hydrolyzed, n value is 4. The experimental n value of about 3, the quantitative yield of formaldehyde and the amount of other products suggest that on the electrolysis at 0.60 V the main reaction route is B and the degree of the hydrolysis of the nitrone is not complete. The reaction scheme for oxidation of hydroxamic acids are as follows.

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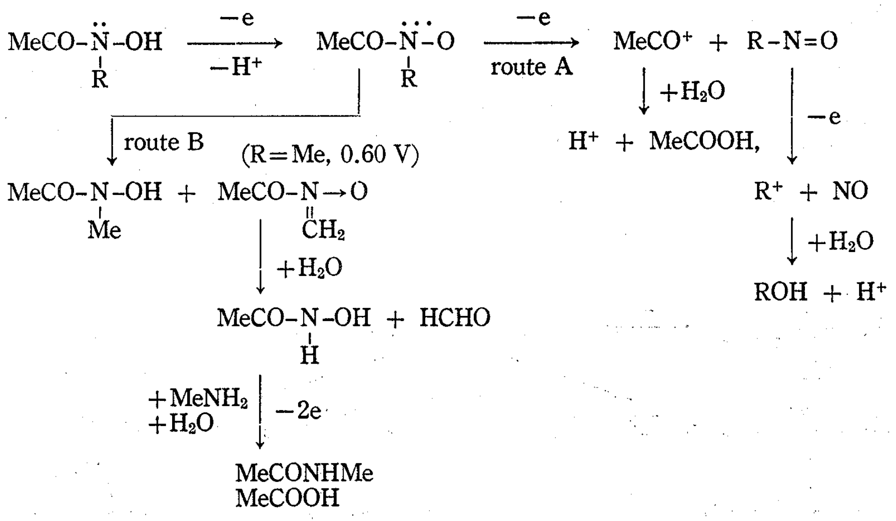
[9] J.H. Cooley, M.W. Mosher, and M.A. Khan, *J. Am. Chem. Soc.*, 90, 1867 (1968).



On oxidation of hydroxamic acids by some chemical oxidants,3) N,O-diacyl-N-alkylhydroxylamine was found to be the main product and this compound acylated added amines. On the other hand, on electrochemical oxidation, the acylation probably involves a free acyl cation and does not a secondary reaction of N,O-diacyl-N-substituted hydroxylamine, because the *n* value was nearly 2. The *n* value for the electrochemical formation of N,O-diacyl-N-alkylhydroxylamine does not exceed 1. It is impossible that the diacyl compound generated on electrolysis is oxidized further to free acyl cation and this cation then acylates a nucleophile such as water or amine, because the peak potentials of N,O-diacetyl-N-methylhydroxylamine and N,O-diacetyl-N-phenylhydroxylamine were considerably more anodic than those of the starting acids, *i.e.*, 2.35 V and 1.90 V, respectively.

The present study shows that on electrochemical oxidation of hydroxamic acids the acyl group is cleaved very easily from the nitrogen atom of the intermediate and behaves as an acylating agent.

Experimental

Materials——Acetonitrile was purified by the method of Mann.10) Benzohydroxamic acid,11) N-phenylacetohydroxamic acid,12) N-methylacetohydroxamic acid,13) N,O-diacetyl-N-methylhydroxylamine,14) N,O-diacetyl-N-phenylhydroxylamine15) and nitrosomethane16) were prepared as described in the literatures. O-Methylbenzohydroxamic acid17) and O-methylacetohydroxamic acid18) were prepared by a slight modification of the procedure described in the literature. Nitrosobenzene,19) N-cyclohexylbenzamide20) and N-methylbenzamide20) were prepared by standard methods. Nitrous oxide was prepared by the method of Gehlen21) and dissolved into acetonitrile. Reagent grade N-methylacetamide, benzoic acid, methyl acetate and methyl benzoate were used without further purification.

The supporting electrolyte, ethyl-tri-*n*-butylammonium tetrafluoroborate was prepared by the method of House.22)

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18) W.N. Fishbein, J. Daly, and C.L. Streeter, *Anal. Biochem.*, **28**, 13 (1969).
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21) H. Gehlen, *Ber.*, **65**, 1130 (1932).
22) H.O. House, E. Feng, and N.P. Peet, *J. Org. Chem.*, **36**, 2371 (1971).

Cyclic Voltammetry——Cyclic voltammetry was carried out as described in the previous paper,[4] with concentration of hydroxamic acids of *ca.* 5 mM.

Controlled Potential Electrolysis——Electrolyses were performed as reported previously[4] with 10—12 mM hydroxamic acid at glassy-carbon electrode in acetonitrile containing 0.1M sodium perchlorate.

Product Analysis——Gas chromatographical analyses were performed in a JEOL-JGC-20KF gas chromatograph packed with P.E.G.20M or Molecular Sieve 5A using 0.5 μl of electrolyzed solution with an internal standard.

Benzoic Acid and Methylbenzoate: When the aromatic product was benzoic acid only, it was estimated from its absorbance at 228 nm ($\varepsilon=11170$, ethanol) after confirming the absence of residual starting material, benzohydroxamic acid, which has nearly the same ultraviolet absorption as benzoic acid. When both benzoic acid and methyl benzoate were produced, the latter was estimated first by gas liquid chromatography (GLC) (P.E.G.20M, 170°) and then the former was estimated by measuring the increase in methylbenzoate after bubbling diazomethane through the solution to convert benzoic acid to methyl benzoate. About 70% of the benzoic acid was converted to methyl benzoate in this way and observed values were corrected appropriately.

Acetic Acid and Methylacetate: Methylacetate was estimated by GLC (P.E.G.20M, 80°). Acetic acid (1—10 mM) was recovered quantitatively as methylacetate on treatment with diazomethane, and methylacetate was measured by GLC.

Amides: N-Methylacetamide was determined by GLC (P.E.G.20M, 170°). N-Methyl- and N-cyclohexylbenzamide were determined from their absorbances at 220 nm ($\varepsilon=11900$, ethanol) and 226 nm ($\varepsilon=10960$, ethanol), respectively. They were obtained by evaporating off the acetonitrile from the solution and extracting the residue with chloroform.

Nitrous Oxide: Nitrous oxide was determined by GLC (molecular sieve 5A, 150°) using the method of Sutton.[23]

Methanol: Methanol was estimated by GLC (P.E.G.20M, 80°).

Nitroso Compounds: Nitrosobenzene and nitrosomethane were determined from their absorbances at 750 nm ($\varepsilon=44$, acetonitrile) and 268 nm ($\varepsilon=9800$, ethanol), respectively.

Formaldehyde: Formaldehyde was determined by the method of Bricker.[24] In the presence of excess methylamine, formaldehyde could not be determined by the chromotropic acid method,[25] because the development of the characteristic color was interferred by the reaction of formaldehyde with methylamine.

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