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Anodic Oxidation of Amines. IX.[1] Anodic Oxidation Process of α-Amino Acids in Aqueous Buffer of pH 10

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Anodic oxidation of α-amino acids with and without a β-hydroxy group was investigated by cyclic voltammetry and controlled potential electrolysis in aqueous carbonate buffer of pH 10. The first wave of the α-amino acids is developed at nearly the same potentials as those observed for the corresponding simple aliphatic amines, showing that a β-hydroxy group does not significantly decrease the first oxidation potential, in contrast to the case of β-alkanolamines. Decarboxylation accompanied by dealkylation is the main reaction process, and a small amount of C–C bond fission also occurs only in the case of the β-hydroxy amino acids.

Keywords——α-amino acid; anodic oxidation; decarboxylation; carbon–nitrogen bond fission; carbon–carbon bond fission; aldehyde; *N*-methyl-α-amino acid; *N*, *N*-dimethyl-α-amino acid

We have previously studied the anodic oxidation of aliphatic amines,[2] β-alkanolamines[3] and ethane-1,2-diamines,[1] and the chlorine dioxide oxidation of amines with an oxymethylene group at the β-carbon in buffer solution of pH 10.[4] Classical oxidative electrochemical degradation under strongly acidic conditions[5] and chemical oxidations of α-amino acids[6] have been reported. These studies, however, were concerned only with estimation of the degraded products and not with the oxidation mechanism. In the present study, we describe the anodic oxidation mechanisms of α-amino acids with and without a β-hydroxy group in buffer solution of pH 10. The amino acids mainly undergo decarboxylation accompanied by C–N bond cleavage, though the amino acids with a β-hydroxy group undergo the (α)C–(β)C bond cleavage to a small extent.

Results and Discussion

Cyclic Voltammetry

The results of cyclic voltammetry of α-amino acids **1**—**12** measured at a glassy-carbon anode in buffer solution of pH 10 are summarized in Table I.

As expected from the pK_1 (2—2.5) and pK_2 (9—10) values of the α-amino acids, the acids are present largely in the ionized form at pH 10. The first wave at E_{p1} can be ascribed to the electron transfer from the amino nitrogen, because the values of E_{p1} decrease markedly with increasing number of alkyl groups on the amino nitrogen, and the amino acids do not show any oxidation wave in acidic solution below pH 8.

The β-hydroxy group of the α-amino acids seems to have essentially no effect on the E_{p1} values, contrary to the case of the anodic oxidation of β-alkanolamines.[3] The oxidation potentials of the amines listed in Table II show that the E_{p1} values of **2**, **6**, **8**, and **11** are little affected by the replacement of a hydrogen with a carboxylate anion.

As will be mentioned in the section on controlled potential electrolysis, the oxidation of

TABLE I. Cyclic Voltammetric Data at pH 10

	Compds.	Volt *vs.* SCE[a] E_{p1}	E_{p2}	E_{p3}
1	$H-\underset{\underset{NH_2}{\vert}}{CH}-COOH$	1.50		
2	$H-\underset{\underset{NHMe}{\vert}}{CH}-COOH$	0.99	1.46	
3	$H-\underset{\underset{NMe_2}{\vert}}{CH}-COOH$	0.71	0.99	1.44
4	$CH_3-\underset{\underset{NH_2}{\vert}}{CH}-COOH$	1.39		
5	$CH_3-\underset{\underset{NHMe}{\vert}}{CH}-COOH$	1.02	1.38	
6	$C_6H_5-\underset{\underset{NHMe}{\vert}}{CH}-COOH$	1.03	1.55	
7	$H-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NH_2}{\vert}}{CH}-COOH$	1.50		
8	$H-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NHMe}{\vert}}{CH}-COOH$	1.04	1.48	
9	$H-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NMe_2}{\vert}}{CH}-COOH$	0.69	1.08	1.44
10	$CH_3-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NH_2}{\vert}}{CH}-COOH$	1.50		
11	$CH_3-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NHMe}{\vert}}{CH}-COOH$	1.03	1.48	
12	$CH_3-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NMe_2}{\vert}}{CH}-COOH$	0.71	1.05	1.40

a) Measured at a substrate concentration of *ca.* 5 mM and a sweep rate of 0.05 V s^{-1}.

TABLE II. Cyclic Voltammetric Data at pH 10

Compds.	Volt *vs.* SCE[a] E_{p1}	E_{p2}
$H-\underset{\underset{NHMe}{\vert}}{CH_2}$	1.08	1.41
$C_6H_5-\underset{\underset{NHMe}{\vert}}{CH_2}$	0.96	1.38
$H-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NHMe}{\vert}}{CH_2}$	1.01	1.53
$CH_3-\underset{\underset{OH}{\vert}}{CH}-\underset{\underset{NHEt}{\vert}}{CH_2}$	1.00	1.51

a) Measured at a substrate concentration of *ca.* 5 mM and a sweep rate of 0.05 V s^{-1}.

N-methyl-α-amino acids gave methylamine as the main product and a small amount of formaldehyde, so the second wave at E_{p2} of *N*-methyl-α-amino acids may be ascribed to the oxidation of both primary amines produced and the carboxylate anion. Simple aliphatic carboxylate anions show an oxidation wave at around the same potential, as was confirmed for heptanoic and acetic acids.

Controlled Potential Electrolysis

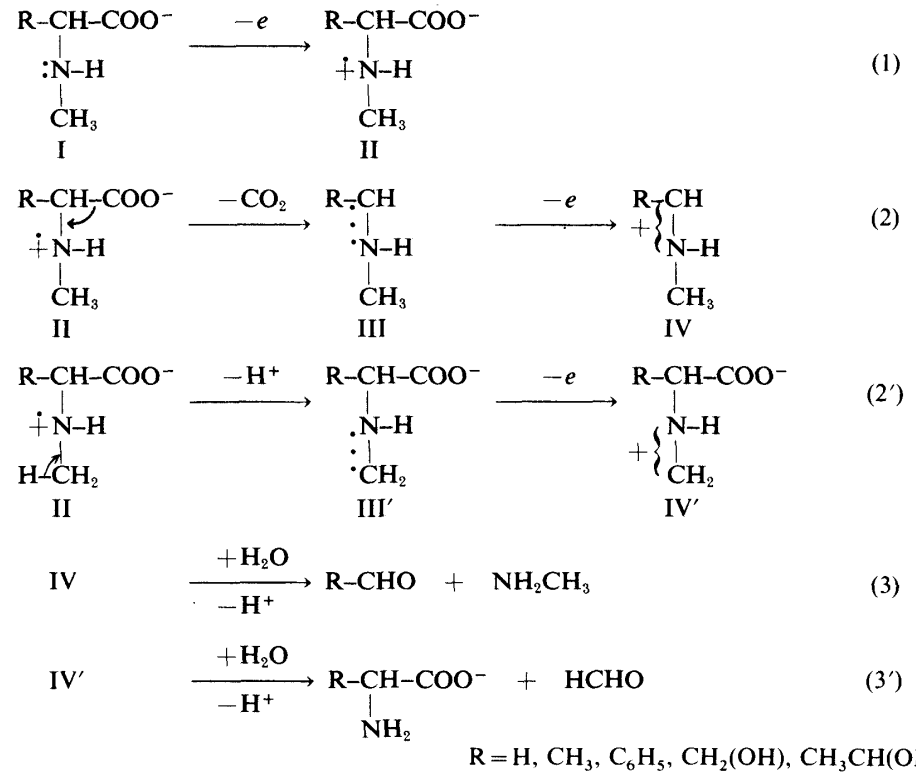
Controlled potential electrolysis in the present study was performed in general using *N*-

Table III. Controlled Potential Electrolysis at pH 10

	Compds.	$E_{app.}$ [a]	F/mol	Products	Yield (%) [b] Mean (Limit)
2	H–CH(NHMe)–COOH	1.00	2.00—2.18	HCHO	59 (4)
				NH_2Me	31 (3)
				CO_2	c)
				H–CH(NH_2)–COOH	3
5	CH_3–CH(NHMe)–COOH	1.00	1.92—2.20	CH_3CHO	97 (6)
				NH_2Me	80 (7)
				CH_3–CH(NH_2)–COOH	3
				HCHO	5 (1)
6	C_6H_5–CH(NHMe)–COOH	1.00	2.01—2.02	C_6H_5CHO	100 (1)
				NH_2Me	93 (1)
				C_6H_5CH(NH_2)COOH	c)
				HCHO	0.7 (0.6)
8	H–CH(OH)–CH(NHMe)–COOH	1.00	2.02—2.07	HCHO	12 (4)
				NH_2Me	82 (4)
				HC(OH)–CHO	23 (4)
				H–CH(OH)–CH(NH_2)–COOH	2
11	CH_3–CH(OH)–CH(NHMe)–COOH	1.00	2.03—2.09	CH_3CHO	10 (5)
				NH_2Me	71 (7)
				HCHO	13 (4)
				CH_3–CH(OH)–CH(NH_2)–COOH	5

a) Applied potential (volt *vs.* SCE).
b) Mol % of starting acid.
c) Detected but not determined.

methyl-α-amino acids, since the oxidation potentials (E_{p1}) of the amino acids with a primary amino group (**1** and **7**) were close to the anodic limit of the background current for the carbonate buffer, and *N*, *N*-dimethyl-α-amino acids such as **3** were not stable, but decomposed to give a considerable amount of dimethylamine when the solution was stirred at room temperature. The results of controlled potential electrolysis performed at a concentration of *ca.* 10 mM at a glassy-carbon plate electrode are summarized in Table III. The electricity consumed per mole of the amino acids suggest that the reaction is a two-electron oxidation. On anodic oxidation of **2**, **5**, and **6**, methylamine and R^1CHO (R^1 = α-substituent) were obtained as the main products with a small amount of the corresponding α-amino acids. The occurrence of decarboxylation was apparent from the results, and estimation of carbon dioxide was tried in the case of the oxidation of **2**. Upon oxidation of the β-hydroxy-α-amino acids **8** and **11**, fairly large amounts of methylamine were formed, though the substituents on the β-carbon are different and the amounts of formaldehyde and acetaldehyde were only about 10%. In the case of **8**, a moderate amount of glycolaldehyde (*ca.* 23%) was detected. The product distributions in the cases of **8** and **11** suggest that the main reaction process of the β-hydroxy amino acids is also decarboxylation accompanied by deaminomethylation. Based on the results of cyclic voltammetry and controlled potential electrolysis, the following reaction processes are suggested to account for the present results.



(1)

(2)

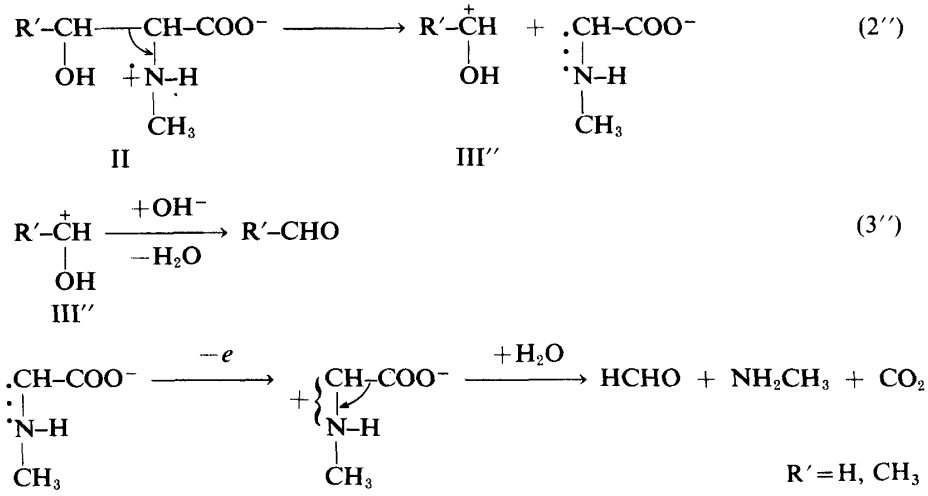
(2′)

(3)

(3′)

R = H, CH_3, C_6H_5, $CH_2(OH)$, $CH_3CH(OH)$

In the case of β-hydroxy α-amino acids, about 10% of the intermediate (II) undergoes (α)C–(β)C cleavage. The results indicate that the fugacity of carbon dioxide is much larger than that of the oxycarbocation (III″) from the cationic α-carbon.



(2″)

(3″)

R′ = H, CH_3

The anodic oxidation of α-amino acids having an R–CH(NH_2)–COOH group in nitric acid has been reported to give a fair amount of oxalic acid.[5] The results show that the acids cleave the C–C bond between R and the α-carbon to the amino group to a considerable extent under acidic conditions in contrast to the present finding at pH 10. At pH 10, the carboxyl group of the α-amino acids is ionized to the carboxylate anion. The loss of carbon dioxide from the cationic reaction center with donation of an electron pair to the cationic part as shown in eq (2) is easier than the loss of CO_2H^+, if it occurs in acidic solution. Step (2″) is not important at all compared to step (2), if there is no β-hydroxy group to stabilize the carbocation portion. A lone pair of electrons of the oxygen in the hydroxy group in **8** and **11** stabilizes the carbocation, and only in these compounds does (α)C–(β)C bond cleavage take

place to some extent, as shown in step (2''). Formaldehyde, methylamine and carbon dioxide are produced by this reaction route to some extent.

The effect of α-substituents, R, on the relative amount of step (2) to step (2') is in the order $H < CH_3 \lesssim C_6H_5$. This order seems to reflect the stability of the radical (III) formed by the loss of carbon dioxide.

Experimental

Reagents——α-Amino Acids: All α-amino acids used in the present study are mixtures of D and L α-amino acids. Commercially available reagent-grade glycine **1**, *N*-methylglycine **2**, *N*,*N*-dimethylglycine **3**, alanine **4**, *N*-methylalanine **5**, serine **7**, and threonine **10** were used without further purification. *N*-Methylphenylglycine **6** was prepared from phenylglycine according to the reported method[7] and purified by column chromatography on ion exchange resin (hydrogen form Amberlite IR-200) then recrystallized from water–acetone. Sublimed at 238 °C (lit.[8] 245—246 °C). *N*-Methylserine **8** and *N*-methylthreonine **11** were prepared by a method similar to that used for **6** from serine **7** and threonine **10**, respectively, and recrystallized from water–ethanol–acetone, mp (**8**) 191 °C, *Anal.* Calcd for $C_4H_9NO_3 \cdot 0.1H_2O$: C, 39.73; H, 7.67; N, 11.58. Found: C, 39.98; H, 7.67; N, 11.62. NMR (D_2O) δ: 2.75 (3H, s, $-CH_3$), 3.64 (1H, t, $J=5$ Hz, $-CH_2-CH-$), 3.98 (2H, d, $J=5$ Hz, $>CH_2$), mp (**11**) 233 °C, *Anal.* Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 44.96; H, 8.47; N, 10.39). NMR (D_2O) δ: 1.26 and 1.37 (3H, s and s, $-CH_3$), 2.72 (3H, s, $-NH-CH_3$), 3.35 (1H, d, $J=7$ Hz, $-CH-NHMe$), 4.03 (1H, q, $J=7$ Hz, $>CH-OH$). *N*,*N*-Dimethylserine **9** was prepared by dimethylation of serine **7** with formaldehyde and sodium cyanoborohydride according to the reported method[9] and purified by column chromatography on ion exchange resin (Amberlite IR-120) then recrystallized from ethanol, mp 170 °C (dec.), *Anal.* Calcd for $C_5H_{11}NO_3$: C, 45.16; H, 8.33; N, 10.52. Found: C, 44.86; H, 8.50; N, 10.45. *N*,*N*-Dimethylthreonine **12** was prepared by the same method as used for the preparation of **9** and recrystallized from methanol, mp 208 °C (dec.) [lit.[10] 208 °C (dec.)].

Apparatus and Procedures——Cyclic Voltammetry: Cyclic voltammetry was performed with a three-electrode system employing a linear scanning unit (Hokuto Denko Co., model HB 101) equipped with a potentiostat (Hokuto Denko Co., model PS-500B). The electrode system consisted of a glassy-carbon indicator electrode (3 mmϕ), a glassy-carbon counter electrode and a saturated calomel electrode (SCE). Measurements were carried out at 25 ± 0.05 °C with a substrate concentration of *ca.* 5 mM and a sweep rate of 0.05 V s^{-1}.

Controlled Potential Electrolysis: Controlled potential electrolysis was carried out with a Hokuto Denko HA 101 potentiostat; the current was recorded on a Toa Dempa EPR-2TB recorder and the quantity of electricity consumed during electrolysis was measured with a Hokuto Denko HF 102 coulombmeter. The anolyte in an H-type electrolysis cell (*ca.* 1×10^{-2} M substrate in carbonate buffer, 20 ml, pH 10.0) was electrolyzed using a glassy-carbon plate electrode (1 cm × 3 cm) with mechanical stirring.

Product Analysis——a) Amines: Amines were analyzed as their sulfonamides[11] in the same manner as described previously.[3]

b) Aldehydes: Benzaldehyde was determined by the method described previously.[12] Formaldehyde was determined by the method of Tanenbaum and Bricker.[13] Acetaldehyde was determined by gas chromatography (GLC) as described previously.[4]

c) Amino Acids: Amino acids were determined fluorophotometrically according to the literature method[14] using 3 ml of the solution after electrolysis.

d) Glycolaldehyde was determined spectrophotometrically according to the literature method.[15] The absorption spectrum of the electrolyzed solution was identical with that of an authentic sample, which had an absorption maximum at 660 nm.

e) Carbon Dioxide: The formation of carbon dioxide during the electrolysis of glycine was confirmed by comparison of the amounts of carbon dioxide contained in the anolyte before and after the electrolysis. Carbon dioxide in the anolyte was introduced into a 5% (w/v) solution of barium hydroxide in a stream of nitrogen to give barium carbonate.

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