Studies on the Autocatalyzed Oxidation of Amino Acids by Peroxomonosulfate

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ABSTRACT: The kinetics of oxidation of six α-amino acids (AA) by peroxomonosulfate (PMS) ion at pH 4.2 and 35°C are investigated once again. The rate of disappearance of peroxomonosulfate at constant [AA] and [H^+] follows the equation

$$-\frac{d[PMS]_t}{dt} = k_1^{obs}[PMS]_t + k_2^{obs}[PMS]_t([PMS]_0 - [PMS]_t)$$

The experimental results suggest that the hydroperoxide intermediate formed by the reaction between the hydrated form of aldehyde and PMS is more reactive and is responsible for the autocatalysis. The hydroperoxide reacts with the amino acid in the rate-determining step. This observation is contrary to the earlier explanation that the autocatalysis is due to the Schiff's base from amino acid and aldehyde. The effect of H^+, the structure of the aldehyde, etc. on the rate constants are discussed. © 2003 Wiley Periodicals, Inc. Int J Chem Kinet 35: 475–483, 2003

INTRODUCTION

The oxidation of α-amino acids (AA) by peroxomonosulfate (PMS) is an interesting area of experimentation in the respect that the reaction is catalyzed by the product aldehyde [1–4]. This observation is explained by the formation of Schiff's base type intermediate due to the reaction between amino acid and aldehyde. In the case of secondary amines, the hemiaminal formed will be transformed into enamines, not to Schiff's base, only if there is alpha hydrogen in the carbonyl compound [5]. Therefore, the kinetics of the oxidation of glycine and *N*-methyl glycine by PMS should differ and we should not observe autocatalysis in the latter. The earlier works were carried out with α-amino acids of unsubstituted amino group and hence only limited information is available. Also, the catalytic effect was studied by adding the product [2–4], and the effect of the aldehyde produced during the course of the reaction is not taken into account. This prompted us to study the oxidation of α-amino acids by PMS in buffered medium (pH ~3.4 to 5.4) at 35°C and the results are presented in this paper.

EXPERIMENTAL

The rates of oxidation of α-amino acids are followed by monitoring the concentration of the unreacted PMS

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by iodometry. The experimental details are given in Ref. [1]. The product of the reaction is determined with equal concentration of amino acid and PMS (usually 0.01 M). The formation of aldehydes is confirmed by 2,4-dinitrophenyl hydrazine method [6]. The percentage yields are

$$\left.\begin{array}{l}\text{Glycine}\\ \text{Alanine}\\ \alpha\text{-Amino-}n\text{-butyric acid}\end{array}\right\} \longrightarrow \quad 95\ (\pm 5)\%\ \text{RCHO}$$

$$\left.\begin{array}{l}\text{Threonine}\\ \text{Serine}\end{array}\right\} \longrightarrow \quad 150\ (\pm 10)\%\ \text{RCHO}$$

determined by hypoiodite method (formaldehyde) [7] and hydroxylamine hydrochloride–pyridine method (acetaldehyde and propionaldehyde) [8]. The percentage yield in threonine and serine is determined by 2,4-dinitrophenyl hydrazine method and the higher yield is due to the formation of osazones [6].

CALCULATIONS

The experimental results suggest that the oxidation of α-amino acids can be represented by the following kinetic scheme.

$$\text{Amino acid} + \text{PMS} \xrightarrow{k_1} \text{Intermediate 1} + {SO_4}^{2-} \tag{1}$$

$$\text{Intermediate 1} + \text{PMS} \longrightarrow \text{Intermediate 2} + {SO_4}^{2-} \tag{2}$$

$$\text{Intermediate 2} + \text{Amino acid} \xrightarrow{k_2} 2\ \text{Intermediate 1} \tag{3}$$

The rate equation under the condition [AA] ≫ [PMS] can be written as

$$-\frac{\mathrm{d[PMS]}}{\mathrm{d}t} = k_1^{\mathrm{obs}}[\mathrm{PMS}] + k_2^{\mathrm{obs}}[\text{Intermediate 1}] \times [\mathrm{PMS}] \tag{4}$$

Further we make an approximation that [Intermediate 1] ≈ $[\mathrm{PMS}]_0 - [\mathrm{PMS}]_t$. Therefore

$$\mathrm{Rate} = -\frac{\mathrm{d}[\mathrm{PMS}]_t}{\mathrm{d}t} = k_1^{\mathrm{obs}}[\mathrm{PMS}]_t + k_2^{\mathrm{obs}}([\mathrm{PMS}]_0 - [\mathrm{PMS}]_t) \times [\mathrm{PMS}]_t \tag{5}$$

The integrated form of this equation can be given as in Eq. (6).

$$[\mathrm{PMS}]_t = \frac{\left(k_1^{\mathrm{obs}} + k_2^{\mathrm{obs}} \times [\mathrm{PMS}]_0\right)}{k_2^{\mathrm{obs}} + \left(\frac{k_1^{\mathrm{obs}}}{[\mathrm{PMS}]_0}\right) \times \exp\left(\left(k_1^{\mathrm{obs}} + k_2^{\mathrm{obs}} \times [\mathrm{PMS}]_0\right) \times t\right)} \tag{6}$$

Equation (6) can be solved nonlinearly to obtain the better estimates of k_1^{obs} and k_2^{obs}. The utility of Eq. (5) is to get the approximate values of k_1^{obs} and k_2^{obs}, which can be used as the initial input for the nonlinear regression. The rate $-\mathrm{d[PMS]}/\mathrm{d}t$ can be calculated by the modified formula of finite-divided difference approximation [9]. The linear as well as the nonlinear regressions were carried out using Sigma plot for Windows (Version 5.0, SPSS Inc.) in an IBM compatible PC with the Windows 98 operating system.

RESULTS AND DISCUSSION

All the kinetics were studied with [AA] ≫ [PMS]. The plots of $[\mathrm{PMS}]_t$ vs. time are approximately linear (Fig. 1) in most of the amino acids and the slope of the plot increases with increase in the initial concentration of PMS, i.e. $[\mathrm{PMS}]_0$. Moreover, when the reaction rate is plotted against time, an increasing curve with an approximate limiting value (Fig. 2) is obtained. The plots $-\mathrm{Rate}/[\mathrm{PMS}]_t$ vs. $[\mathrm{PMS}]_t$ are linear (Fig. 3). These observations suggest that the oxidation of amino acids by PMS follows the autocatalyzed mechanism as given in Eq. (5). The rate constants for the oxidation of amino acids (k_1^{obs}) and the autocatalyzed part (k_2^{obs}) are calculated by the nonlinear regression of Eq. (6) and only these values are used for analyzing the experimental results.

The values of k_1^{obs}, at constant pH, increase with amino acid concentrations and the plots k_1^{obs} vs. [AA] give straight lines, with negligible positive or negative intercept that can be approximated as passing through the origin. This observation leads to the conclusion that the rate-limiting step involves the amino acid also. The values of k_1^{obs} first decrease and then slightly increase with decrease in pH (range ~3.5 to 5.5). A reasonably better correlation between k_1^{obs} and $[\mathrm{H}^+]$ is shown (Fig. 4) by the relation $k_1^{\mathrm{obs}} = A \times [\mathrm{H}^+] + \frac{B}{[\mathrm{H}^+]}$.

The k_2^{obs} values also increase with amino acid concentrations and the plots of k_2^{obs} vs. [AA] are linear with negative intercept in all the amino acids studied. The relation between k_2^{obs} and [AA] can be represented by the equation $k_2^{\mathrm{obs}} = k_2'([\mathrm{AA}] - [\mathrm{AA}]_0)$. This equation

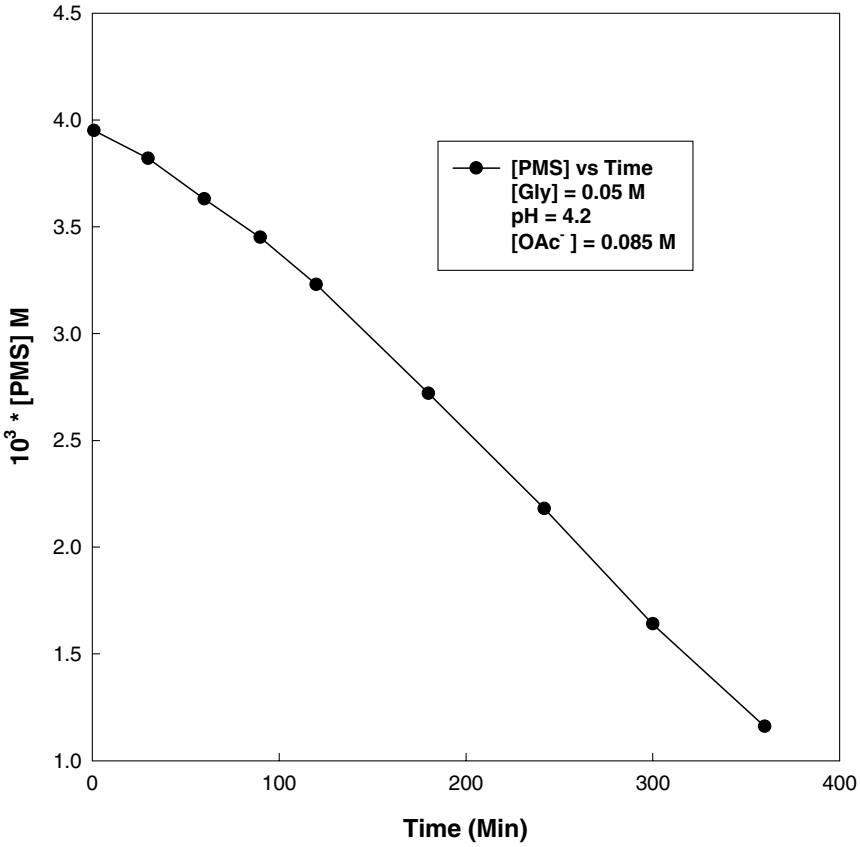


Figure 1 Plot of [PMS] vs. time.

suggests that the catalytic effect can be observed only when the [AA] is greater than a critical value $[AA]_0$. The calculated critical concentrations are tabulated in Table I. The perusal of the results in Table I suggests that the critical concentration of alanine and α-amino-*n*-butyric acid is higher than other amino acids and hence the catalytic part of the reaction can be observed only when [AA] > 0.1 M. This is confirmed by studying the oxidation with [AA] = 0.5 M wherein a first-order kinetics is observed. Studies on the effect of $[H^+]$ on k_2^{obs} show that an inverse relationship between k_2^{obs} and $[H^+]$ exists in all the amino acids. The catalytic effect of acetate ion on the rate constants is observed at the pH approximately >4.6. Therefore all the kinetics are studied at a constant $[OAc^-]$ (0.085 M).

Table I Critical Concentrations for the Autocatalysis

Amino Acid	$[AA]_0$ (M)
Glycine	0.037
N-Methyl glycine	0.015
Alanine	0.092
α-Amino-*n*-butyric acid	0.093
Serine	0.042
Threonine	0.031

In aqueous solution, peroxomonosulfate exists as a mixture of HSO_5^- and SO_5^{2-} because of the equilibrium in Eq. (7).

$$HSO_5^- \overset{K_d}{\rightleftharpoons} SO_5^{2-} + H^+ \tag{7}$$

The K_d value is reported [10] as 4.0×10^{-10} M at 25°C and under the experimental conditions (in the pH range ~3.5 to 5.2) PMS will exist as HSO_5^-.

Aliphatic amino acids exist in the following equilibrium.

$$RCH(\overset{+}{N}H_3)COOH \overset{-H^+}{\rightleftharpoons} RCH(\overset{+}{N}H_3)COO^- \overset{-H^+}{\rightleftharpoons} RCH(NH_2)COO^- \tag{8}$$

The pK_{a_1} values for the amino acids [11] used in this study are ≤2.35. The pH of the reaction was maintained at ~4.2 and the influence of $[H^+]$ ion was studied starting from pH 3.5. Therefore, amino acids will

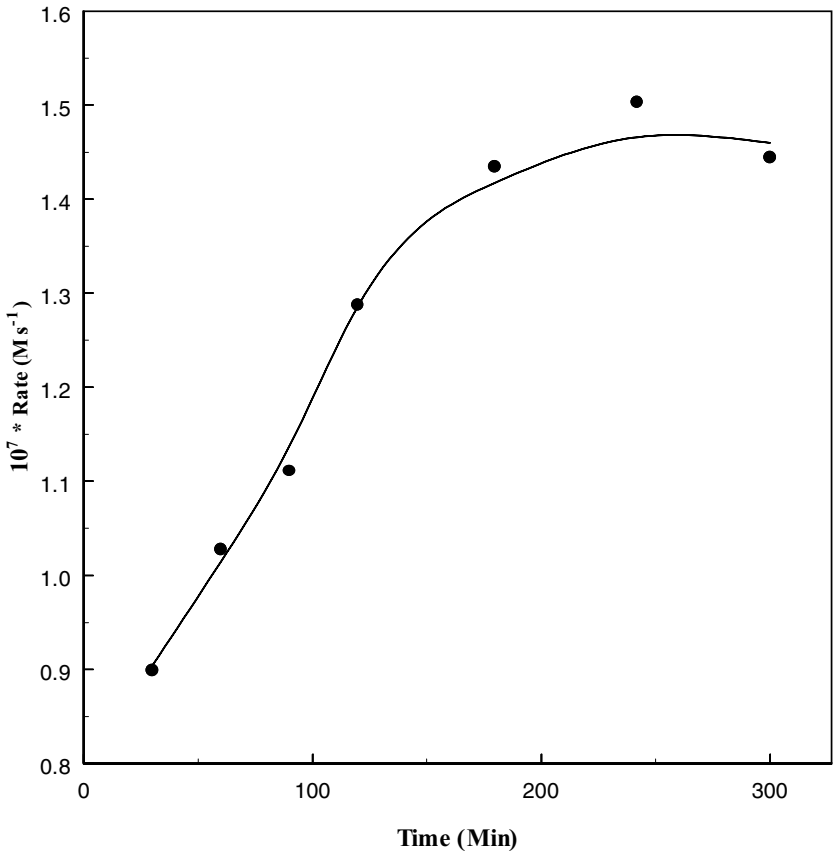


Figure 2 Plot of rate vs. time for the data in Fig. 1.

exist mainly as the dipolar zwitterionic form.

$$\text{R-CH}(\overset{+}{\text{N}}\text{H}_3)\text{-COO}^- + \text{HOOSO}_3^- \underset{}{\overset{K_1}{\rightleftharpoons}} \text{R-}\underset{\displaystyle \text{COO}^-}{\underset{|}{\text{CH}}}\text{-}(\text{NH}_3)\text{-OOSO}_3^-) + \text{H}^+ \quad \text{(I)} \quad (9)$$

$$\text{(I)} \xrightarrow{k_1} \text{Product} \quad (10)$$

$$\text{R-CH}(\overset{+}{\text{N}}\text{H}_3)\text{-COOH} + \text{HOOSO}_3^- \xrightarrow{k_1^{\text{H}}} \text{Products} \quad (11)$$

$$\text{R-CH}(\overset{+}{\text{N}}\text{H}_3)\text{-COO}^- + \text{HOOSO}_3^- \xrightarrow{k_1'} \text{Products} \quad (12)$$

The observed experimental results for the oxidation of amino acids by PMS (represented by k_1^{obs}) can be generalized as Eqs. (9)–(12). The rate equation for the above reaction sequence can be written as

$$-\frac{\text{d[PMS]}}{\text{d}t} = \left(\frac{K_1 \times k_1[\text{AA}]}{[\text{H}^+]} + \frac{k_1^{\text{H}}}{Kd_1} \times [\text{AA}] \times [\text{H}^+] + k_1' \times [\text{AA}]\right) \times [\text{PMS}] \quad (13)$$

$$\therefore k_1^{\text{obs}} = \frac{K_1 \times k_1[\text{AA}]}{[\text{H}^+]} + \frac{k_1^{\text{H}}}{Kd_1} \times [\text{AA}] \times [\text{H}^+] + k_1' \times [\text{AA}] \quad (14)$$

Kd_1 in Eq. (13) denotes the dissociation constant of the amino acid cation $\text{RCH}(^+\text{NH}_3)\text{COOH}$. The various kinetic constants calculated are tabulated in Table II. It is well known that peroxides/peroxide anions can react through nucleophilic mechanism [12]. Experimental results show that peroxyanions are strongly nucleophilic and SO_5^{2-} is more reactive (approximately six orders of magnitude) than HSO_5^-

Table II Kinetic Constants for the Oxidation of Amino Acids

Amino Acids	$\frac{10^2 \times k_1^{\text{H}}}{K\text{d}_1}$	$10^9 \times K_1 \times k_1$	$10^4 \times k_1'$
Glycine	90.2	21.3	–
Alanine	75.7	4.4	5.4
α-Amino butyric acid	251.0	26.5	–
Serine	225.0	55.9	–
Threonine	349.4	96.0	–
N-Methyl glycine	n.d.	201.0	–

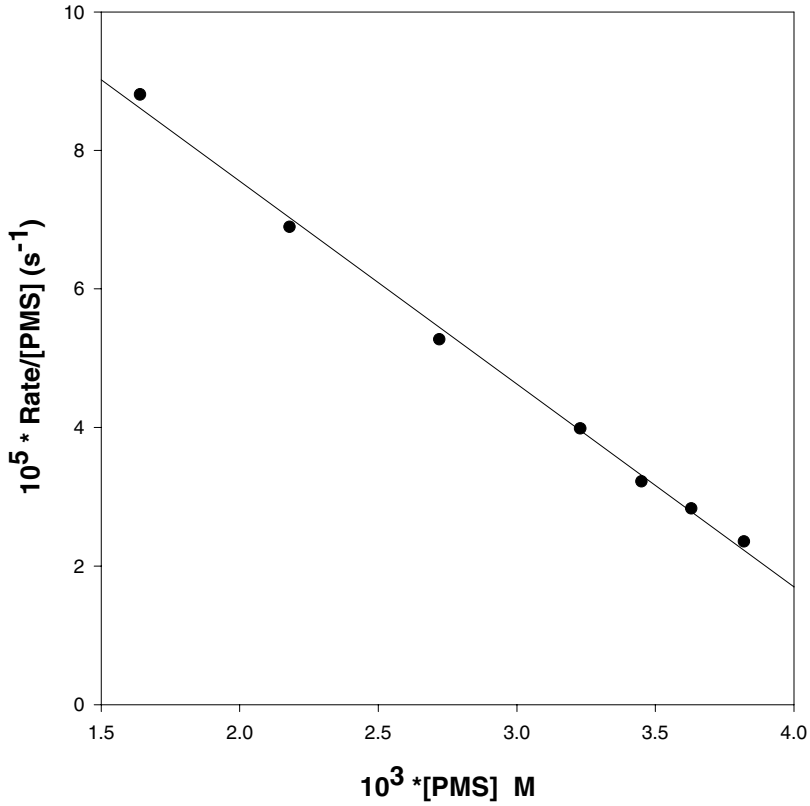


Figure 3 Plot of (rate/[PMS]) vs. time for the data in Fig. 1.

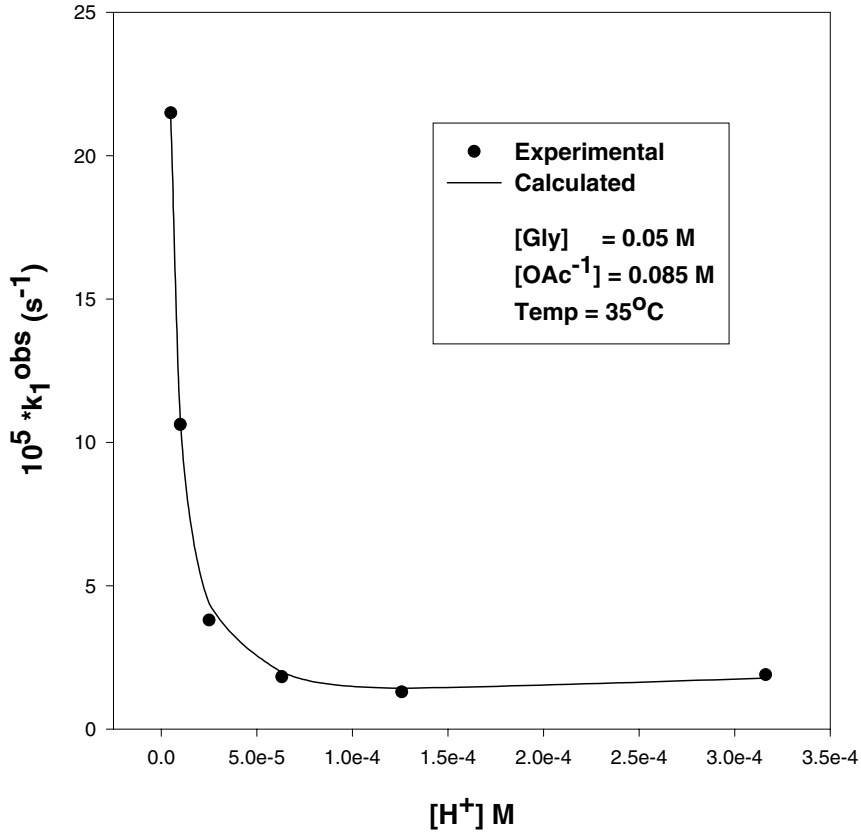


Figure 4 Plot of k_{obs} vs. $[H^+]$.

toward the nucleophilic attack [13]. The first step represents the nucleophilic interaction of the peroxide at the $-NH_3^+$ group. This is equivalent to the reaction of peroxomonosulfate dianion with the electrophile $-NH_3^+$. The second and third steps (Eqs. (11) and (12)) represent the electrophilic interaction of the peroxide molecule. The peroxide oxygen is electronically saturated and less polarizable. Therefore, it is more difficult for the carboxylate ion to approach the peroxide oxygen. This repulsion can be reduced by the presence of H^+ ion. This means that the $-COOH$ group may be more reactive than the $-COO^-$ group.

Perusal of the results in Table II shows that there is no correlation between the rate constants and the structure of the amino acids. The oxidation of amino acid through the carboxylate group (Eq. (12)) is observed only in alanine. This can be explained as follows. The breakdown of the complex may proceed through the nonconcerted process in which carbon–carbon bond cleavage is to precede carbon–nitrogen bond formation. Thus the partial positive charge developed on the α-carbon in the activated state is stabilized by the electron-releasing/donating methyl groups thereby favoring the reaction. If it is so, one would expect that the reaction should occur in α-amino butyric acid also. However, we have not observed the rate constant. This may be due to the fact that the contributions from the reactions (10) and (11) (Table II) are significant in α-amino butyric acid and hence with the limited experimental points we could not calculate k_1' by nonlinear regression.

The oxidation of 2-methyl alanine by PMS was also carried out at 35°C. The results showed that the oxidation is a perfect first-order with respect to each [PMS] and 2-methyl alanine concentration. The oxidation of 2-methyl alanine differs from alanine only in the final product where aliphatic ketone (acetone) is obtained. Even the added acetone has no effect on the rate of oxidation of 2-methyl alanine. Therefore, the methyl substitution at the α-carbon atom of alanine removes the autocatalysis. This suggests that the reaction between aldehyde and PMS is responsible for the autocatalytic effect.

The autocatalytic effect is observed in all the amino acids including *N*-methyl glycine. In fact the critical concentration for *N*-methyl glycine is the lowest one (Table I). This suggests that the contribution from the catalytic path is more significant in *N*-methyl glycine than in other amino acids. The proportion of the catalytic pathway with respect to the total reaction can be calculated from the ratio of the rate of the catalytic pathway (r_c) to the total rate (r) from Eq. (5).

$$\frac{r_c}{r} = k_2^{obs}\left(\frac{[PMS]_0 - [PMS]_t}{\left(k_1^{obs} + k_2^{obs}([PMS]_0 - [PMS]_t\right)}\right) \quad (15)$$

The ratio ($\frac{r_c}{r}$) varies within the limits given by Eqs. (16) and (17).

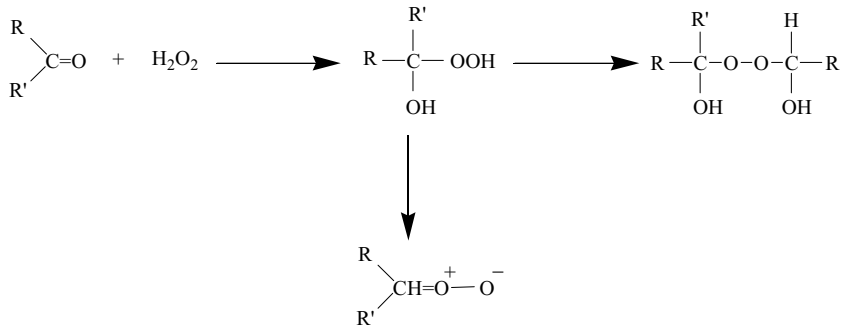
$$\lim_{t \to 0} \left(\frac{r_c}{r}\right) = 0 \quad (16)$$

$$\lim_{t \to \infty} \left(\frac{r_c}{r}\right) = \left(\frac{k_2^{obs}[PMS]_0}{\left(k_1^{obs} + k_2^{obs}[PMS]_0\right)}\right) \quad (17)$$

Thus ($\frac{r_c}{r}$) is plotted against time for glycine, *N*-methyl glycine, alanine, and α-amino-*n*-butyric acid (Fig. 5). In all the cases $[PMS]_0 = 3.8\ (\pm 0.1) \times 10^{-3}$ M and ~75% conversion of the oxidant is followed. The limiting value is 0.96 in glycine and decreases to 0.88 in *N*-methyl glycine.This decrease is due to a large increase in k_1^{obs} (~12 times) relative to the increase in k_2^{obs} (~4 times). This suggests that the substitution of electron-donating methyl group at the nitrogen (reaction center) enhances oxidation by both HSO_5^- and the intermediate. The observed limits r_c/r in alanine and α-amino-*n*-butyric acid are ~0.62 and ~0.40. Even though the substitution of electron-donating groups at the α-carbon enhances k_1^{obs} (~2 to 3 times), there is a large decrease in k_2^{obs} values (~8 to 15 times). The oxidation products resulting from these amino acids are aliphatic aldehydes namely formaldehyde, acetaldehyde, and propionaldehyde. Thus, +I group substitution at the carbonyl group results in a large decrease in the reactivity of the intermediate and this will explain why the critical concentration $[AA]_0$ increases.

The foregoing discussions suggest that the catalytic reaction occurs in all the amino acids studied in this report and the relative importance depends upon the reactivity of the intermediate resulting from the product aldehyde and PMS. Further the substitution at the amino group is in no way inhibiting the catalytic reaction and in fact quickens the catalytic process. This suggests that the formation of Schiff's base type intermediate between the amino acid and the corresponding aliphatic aldehyde may not be the probable mechanism for the autocatalysis.

The formation of relatively stable and water-soluble hydroperoxides from aliphatic carbonyl compounds have already been reported [14,15]. The hydroxyl hydroperoxides are the main products when equimolar quantities of aldehyde and hydrogen peroxides are used, and α,α-dihydroxy peroxides are produced when excess aldehyde is used.



Since peroxomonosulfate can be considered as the derivative of hydrogen peroxide, the formation of hydroperoxides can be considered as the reactive intermediate (Fig. 6) in this study. The first step is the interaction of the hydrated carbonyl compound with HSO_5^- to give the hydroperoxide. This reaction is similar to the reaction of alcohols with H_2O_2 [16]. The second step is similar to the reaction of primary and secondary amines with hydroperoxides to give imines [16]. The observed instability constant K_d [17] for the hydration is highest in acetone

$$\mathrm{RCH(OH)_2} \overset{K_d}{\rightleftharpoons} \mathrm{RCHO} + \mathrm{H_2O}$$

($\sim 5 \times 10^2$) and the least in formaldehyde ($\sim 5.5 \times 10^{-4}$) and the observed order is acetone $\gg$ propionaldehyde $>$ acetaldehyde $\gg$ formaldehyde. Therefore, the concentration of hydrated acetone is negligible and this will explain why autocatalysis is not observed in the

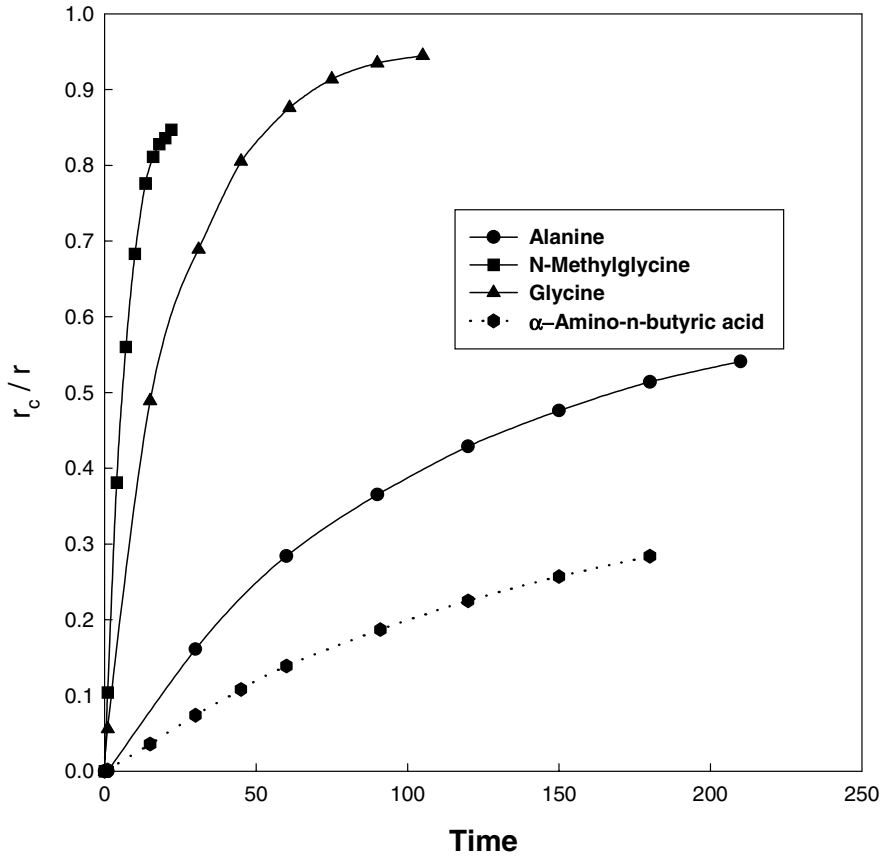


Figure 5 Plot of r_c/r. [AA] = 0.1 M, pH 4.2, [OAc^-] = 0.085 M.

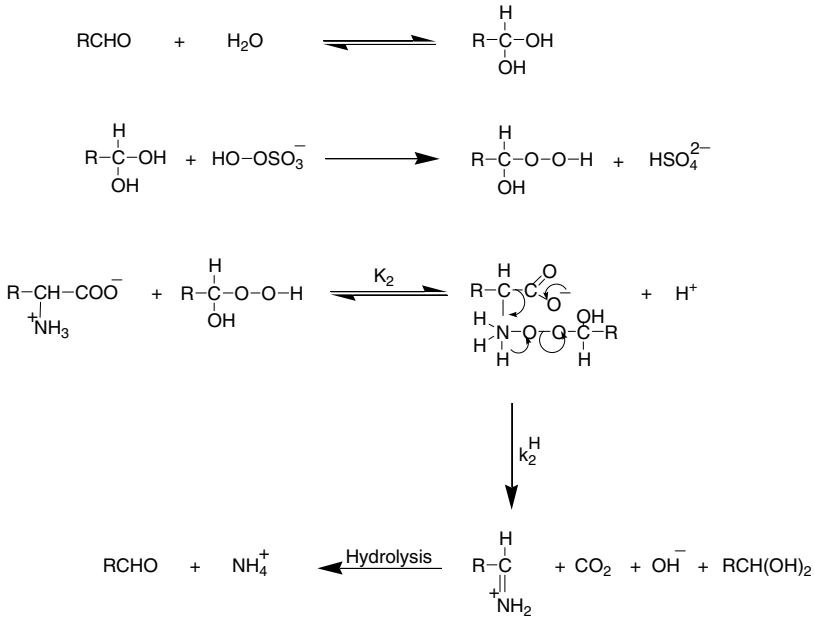


Figure 6 Mechanistic scheme for hydroperoxide-mediated oxidation.

oxidation of α-amino isobutyric acid even in the presence of added acetone. The autocatalyzed reaction can be represented as

$$\text{RCHO} + \text{PMS} \xrightarrow{k_2^0} \text{Hydroperoxide} \xrightarrow{k_2'} \text{RCHO} \quad (18)$$

where $k_2' = k_2 \times [\text{AA}]$ since $[\text{AA}] \gg [\text{PMS}]$. The experimental results suggest that k_2' is the rate-limiting step and hence the rate of disappearance of hydroperoxide becomes

$$-\frac{\text{d}[\text{Hydroperoxide}]_t}{\text{d}t} = k_2' \times [\text{PMS}]_t \times [\text{RCHO}]_t \quad (19)$$

Here we make an assumption that $[\text{Hydroperoxide}]_t$ is very small and hence $[\text{Oxidant}]_t \approx [\text{PMS}]_t$. This explains the reason for using Eq. (5) for the calculation of k_2^{obs}. Based on the experimental results we can propose the following mechanism for the reaction of hydroperoxide with amino acids.

$$\text{R-CH-}(\overset{+}{\text{N}}\text{H}_3)\text{-COO}^- + \text{ROOH} \rightleftharpoons[K_2] \text{R-CH-}(\text{NH}_3\text{OOR})\text{-COO}^- + \text{H}^+ \quad (20)$$

$$\text{R-CH-}(\text{NH}_3\text{OOR})\text{-COO}^- \xrightarrow{k_2^{\text{H}}} \text{Products} \quad (21)$$

$$\therefore k_2^{\text{obs}} = K_2 \times k_2^{\text{H}} \times ([\text{AA}] - [\text{AA}]_0)/[\text{H}^+] \quad (22)$$

Here we have used the term $([\text{AA}] - [\text{AA}]_0)$ since the catalytic part is observed only when [AA] is greater than the critical concentration $[\text{AA}]_0$. From the available data the best kinetic parameters are tabulated in Table III.

Analysis of the results in Table III shows that there is a correlation between $K_2 \times k_2^{\text{H}}$ and the σ^* value for substituents group at the carbonyl carbon of the aldehyde. The $K_2 \times k_2^{\text{H}}$ values are larger with the electron-releasing substituents CH_3— and CH_3—CH_2—. The correlation between $\log(K_2 k_2^{\text{H}})$ and σ^* obeys the relationship.

$$\log\left(K_2 k_2^{\text{H}}\right) = -2.05\ (\pm 0.1) - 1.87\ (\pm 0.36)\,\sigma^* \quad (r = 0.949, N = 5) \quad (23)$$

In the above correlation the data point corresponding to *N*-methyl glycine is excluded. The oxidation product from glycine and *N*-methyl glycine is formaldehyde.

Table III Kinetic Constants for the Catalyzed Oxidation

Amino Acids	$10^6 \times K_2 \times k_2^{\text{H}}$	σ^*
Glycine	150.3	0.49
N-Methyl glycine	402.9	0.49
Serine	135.0	0.31
Threonine	596.8	0.12
Alanine	1072.4	0.00
α-Amino-*n*-butyric acid	1322.4	−0.10

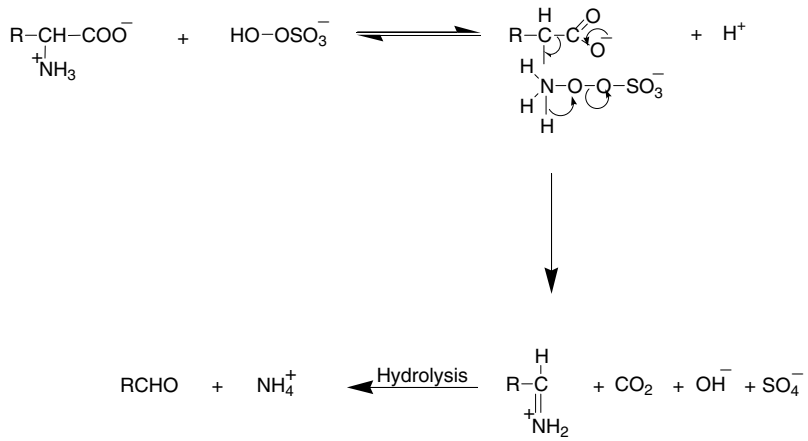


Figure 7 Mechanism for the oxidation by PMS.

Therefore, one would expect that the $(K_2 \times k_2^{H})$ values for glycine and *N*-methyl glycine should be equal but *N*-methyl glycine reacts almost ~2.5 times faster than glycine. The higher reactivity may be due to the inductive effect of the methyl group present at the reaction center (nitrogen atom).

Comparison of the results in Tables II and III shows that the rate of the reaction by HSO_5^- and by hydroperoxide differs by a factor of ~4. The mechanistic scheme shown in Figs. 6 and 7 suggests that the only difference is the leaving group. Therefore, difference in the reactivity of nucleofuge, in addition to the oxidizing power if any, may be the reason for the higher rate of oxidation by hydroperoxides.

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