

Kinetics of Oxidation of Amino Acids with Acid Bromate

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The oxidation of glycine, L-alanine, L-leucine, L-isoleucine and L-phenylalanine by acidified potassium bromate in aq. acetic acid medium is first order each in $[\text{Br(V)}]$ and $[\text{amino acid}]$ and second order in $[\text{H}^+]$. The products of oxidation have been characterised as the corresponding aldehydes, ammonium ion and carbon dioxide. Electron-releasing substituents on the carbon carrying the amino group impede the rate of reaction. The results have been rationalised based on inductive effects and Taft's constants. A mechanism involving the interaction between H_2BrO_3 and the amino acid molecules has been suggested. The substituent effects suggest that the heterolyses of the C-H and the N-H bonds are important factors in the rate-determining step.

Many reports are available in the recent literature on the kinetics of oxidation of amino acids by a variety of metal and non-metal oxidants¹⁻⁵. However, potassium bromate, which is found to smoothly oxidise a number of amino acids in acid medium, has not been used as an oxidant from the kinetic stand point. We report in this paper the kinetics of oxidation of glycine, L-alanine, L-leucine, L-isoleucine and L-phenylalanine by this oxidant in aqueous acetic acid medium in the presence of sulphuric acid.

Materials and Methods

Potassium bromate (AR, BDH) was dried in an air oven at 110°C, cooled and preserved in a desiccator. Purified acetic acid was used. L-Alanine, L-isoleucine and L-phenylalanine were gift samples from Hoechst, USA. All other chemicals used were AR(BDH) samples.

The experiments were carried out under pseudo-first order conditions in aqueous acetic acid (50%, v/v) in the presence of sulphuric acid and the progress of the reaction was followed by estimating unreacted bromate iodometrically at regular time intervals. To avoid complications due to the formation of bromide ion in solution, all the experiments were carried out in the presence of mercuric acetate. Its presence did not affect the rate constants. All the rate constants were reproducible within $\pm 3\%$. The pseudo-first order rate constant, k_1 was obtained from $\log(a-x)$ versus time plot by the method of least squares.

With each amino acid, NH_4^+ in solution, carbon dioxide and the corresponding aldehyde were detected. Each aldehyde was isolated from the reaction mixture by ether extraction and its identity confirmed by standard procedures.

Results and Discussion

The kinetic results can be summarised as follows:

(i) All the reactions are first order in $[\text{oxidant}]$ and the plots of $\log[\text{bromate}]$ versus time are linear for at least 80% of the reaction. The pseudo-first order rate constants obtained by the method of least squares for glycine are reported in Table 1.

(ii) The plots of $\log k$ versus $\log[\text{amino acid}]$ for varying initial $[\text{amino acid}]$ are linear with unit slopes indicating first order dependence on $[\text{amino acid}]$. This is supported by the constancy of k_2 values ($k_2 = k_1/[\text{amino acid}]$). For example, under the conditions $[\text{H}_2\text{SO}_4] = 0.5 \text{ mol dm}^{-3}$, $[\text{bromate}] = 0.001 \text{ mol dm}^{-3}$ and temp. 40°C, $10^5 k_1$ values are 5.62, 7.14 and 8.81 s^{-1} and $10^3 k_2$ values are 2.25, 2.24 and $2.28 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at $10^2 [\text{glycine}] = 2.50, 3.19$ and 3.86 mol dm^{-3} respectively. (iii) No reaction occurred in acetic acid, in the absence of sulphuric acid. The rate constants at varying $[\text{H}_2\text{SO}_4]$, other conditions remaining the same, are given in Table 1. The plot of $\log k_2$ versus $\log[\text{H}^+]$, is linear with a slope of two. An attempted correlation between $\log k_2$ and H_o has not

Table 1—Dependence of Rate on $[\text{Bromate}]$ and $[\text{Sulphuric Acid}]$

$[\text{Glycine}]$: $0.025 \text{ mol dm}^{-3}$; solvent = aq. acetic acid (50%, v/v); temp. = 40°C

$[\text{H}_2\text{SO}_4]$ (mol dm^{-3})	$10^3 [\text{Bromate}]$ (mol dm^{-3})	$10^5 k_1$ (s^{-1})	$10^3 k_2$ ($\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$)	k_2 $[\text{H}^+]^2$
0.50	1.00	5.62		
0.50	3.00	5.47		
0.50	4.00	5.60		
0.50	5.00	5.64		
0.75	1.00		3.86	6.86
1.00	1.00		6.84	6.84
1.25	1.00		10.4	6.66
1.50	1.00		15.0	6.67

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Table 2—Arrhenius Parameters for Bromate Oxidation of Different Amino Acids

Substrate	[Solvent = 50% HOAc, (v/v)]				
	$10^3 k_2$ (50°C) (dm ³ mol ⁻¹ s ⁻¹)	E_a (kJ mol ⁻¹)	$\Delta H^\ddagger$ (kJ mol ⁻¹)	$\Delta G^\ddagger$ (kJ mol ⁻¹)	$\Delta S^\ddagger$ (J mol ⁻¹ K ⁻¹)
Glycine	5.13	75.4	72.7	93.6	-64.5
L-Alanine	0.66	81.0	78.3	99.1	-64.3
L-Leucine	1.05	77.0	74.3	97.8	-72.8
L-Isoleucine	1.30	76.3	73.6	97.3	-73.3
L-Phenylalanine	2.39	76.9	74.3	95.6	-66.1

given satisfactory results. The disappearance of bromate with time in the oxidation of these amino acids can be expressed by Eq.(1).

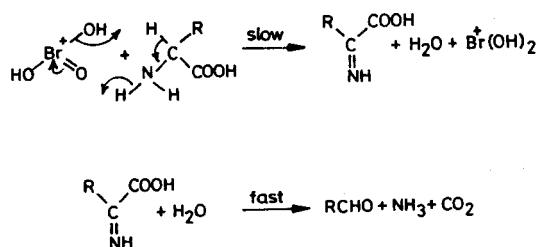
$$-\frac{d[\text{BrO}_3^-]}{dt} = k[\text{bromate}][\text{amino acid}][\text{H}^+]^2 \dots (1)$$

(iv) In 30, 40, 50, 60 and 70% (v/v) aq. acetic acid at 40°C, the $10^3 k_2$ values for glucine-bromate reaction are 0.58, 1.28, 2.25 4.73 and 13.7 dm³ mol⁻¹ s⁻¹ respectively. Thus, increase in the percentage of acetic acid in the reaction medium increases the rate, which may be due to the less polar character of the transition state compared to the reactants. The plot of $\log k_2$ versus $1/D$ is linear, with a positive slope indicating the reaction to be a positive ion-dipole type.

(v) The kinetics of oxidation of glycine, L-alanine, L-leucine, L-isoleucine and L-phenylalanine have been investigated in the temperature range 40 to 60°C and the Arrhenius activation parameters are reported in Table 2. The order of reactivities is as follows: glycine > phenylalanine > isoleucine > leucine > alanine. The five amino acids may be considered as a series of related substituted molecules with the general formula R.CH(NH₂).COOH. With reference to substituents (R) the reactivity order is H > benzyl > *s*-butyl > isobutyl > methyl. It appears that greater the electron density at the reaction site, lesser is the ease of oxidation of amino acid.

Mechanism

Since the order in $[\text{H}^+]$ is two, it is assumed that the effective oxidant species is H_2BrO_3 , as has been observed in the oxidation of secondary alcohols⁶, α -hydroxy acids⁷, cyclanols⁸ and phenols⁹ by acid bromate. Generally, the oxidation of amino acids involves the cleavage of a C—H bond as well as of an N—H bond in the rate-determining step. This is well-substantiated by the results with several oxidants^{1,2,10,11}. Therefore, in the bromate oxidation also cleavage of C—H and N—H bonds might be taking place in the rate-determining step, in which a concerted transfer of electrons is assumed in the interaction between H_2BrO_3 and a molecule of an amino acid as shown in Scheme 1.



Scheme 1

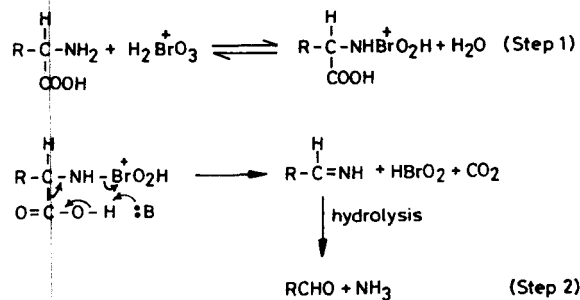
The imino acid produced in the slow step is likely to undergo hydrolysis in a fast step in aqueous mineral acid to give the aldehyde. Attempts to detect and isolate the intermediate imino acid and its hydrolysis product, RCOCCOOH have not been successful. Probably, the imino acid intermediate is highly transient.

Though both the heterolytic cleavage of a C—H bond giving H^+ and of a N—H bond giving H^- occur in the rate-determining step simultaneously, the type of substituents would influence the precedence of one cleavage over the other. With glycine and phenylalanine the cleavage of C—H bond, releasing H^+ is likely to precede that of N—H bond releasing H^- . Hence the data for these two substrates would better be interpreted in terms of electron-withdrawing nature of the substituent groups (R), (Taft values¹¹ H = +0.490 and benzyl = +0.215) favouring cleavage of C—H bond. This accounts for higher reactivity of these two compounds. The substituents, *s*-butyl, isobutyl and methyl are expected to reduce the reactivity of the substrates bearing these groups, i.e. isoleucine, leucine and alanine (Taft values: methyl, 0.0, isobutyl, -0.125 and *s*-butyl, -0.210). However, among them the reactivity order is: isoleucine > leucine > alanine or in other words *s*-butyl > isobutyl > methyl. This could be explained on the assumption that in these substrates the heterolysis of N—H bond releasing H^- precedes that of C—H bond releasing H^+ .

No linearity is observed¹² in the plots of $\log k/k_0$ versus σ^* , $\log k/k_0$ versus E_a and $\log k/k_0 - E_a$ versus σ^* . This also rules out any predominant operation of

steric effect influencing the reactivity. Hence a mechanism involving preferential cleavage of either C-H or N-H bond is justified.

Another possible mechanism (Scheme 2) similar to that suggested for bromate oxidation of α -hydroxy acids may be considered⁷.



Scheme 2

Unlike in the case of oxidation of α -hydroxy acids, where the reaction is insensitive to substituent effects, in the present study the reaction exhibits a dominant structural influence indicating that the first step, i.e. formation of bromate ester assumed by earlier workers⁷ cannot be the rate-determining step. The decomposition of this bromate-ester type complex leading to the imine (step 2)—similar to the one suggested by Westheimer in the oxidation of secondary alcohols by chromic acid¹³—being a slow step is also unlikely, since if it were so the entropy of activation

would not be as negative as has been observed in our study. Considering these arguments a mechanism similar to that proposed for bromate oxidation of α -hydroxy acids may be ruled out.

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References

- 1 China Rajanna & Saiprakash P K, *Indian J Chem*, **18A** (1979) 412.
- 2 Bhargava M, Sethuram B & Navaneeth Rao T, *Indian J Chem*, **16A** (1978) 651.
- 3 Katgeri S N, Mahadevappa D S & Naidu H M K, *Indian J Chem*, **19A** (1980) 29.
- 4 Mahadevappa D S, Ahmed M S & Gowda N M M, *Indian J Chem*, **19A** (1980) 325.
- 5 Manikyamba P & Sundaram E V, *Indian J Chem*, **19A** (1980) 1122.
- 6 Natarajan R & Venkatasubramanian N, *Tetrahedron Lett*, **57** (1969) 5021.
- 7 Natarajan R & Venkatasubramanian N, *Int J chem Kinetics*, **8** (1976) 205.
- 8 Natarajan R & Venkatasubramanian N, *Indian J Chem*, **17A** (1979) 257.
- 9 Vijayalakshmi & Sundaram E V, *Indian J Chem*, **15A** (1977) 612.
- 10 Bose A K, Mehrotra R M & Mushran S P, *Indian J Chem*, **11A** (1973) 896.
- 11 Wiberg K B, *Physical organic chemistry*, (John Wiley, New York), 1946, 415.
- 12 Richard D Gilliam, *Introduction to physical organic chemistry*, (Addison-Wesley, New York), 1970, 159.
- 13 Westheimer F H & Nicolaides N, *J Am chem Soc*, **71** (1949) 25.