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Kinetics & Mechanism of Oxidation of Some α-Amino Acids by Phenyliodosyl Acetate & Lead Tetraacetate: A Comparative Study

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Second order rate constants in the phenyliodosyl acetate oxidation of glycine, L-phenylalanine, L-leucine, L-valine and L-alanine in aqueous acetic acid in the presence of perchloric acid are reported. Inverse unit dependence on $[H^+]$ has been observed for all the substrates except for glycine which shows inverse fractional order dependence in $[H^+]$. Increase in the proportion of acetic acid in solvent medium retards the rate. Added NaOAc accelerates the rate upto a concentration of 0.02 mol dm^{-3}, thereafter further variation in [NaOAc] has marginal effect. For comparison, the lead tetraacetate oxidation of these substrates has also been studied. Activation parameters have been computed. The acid independent rate constants for PIA oxidation in 10% and 95% HOAc and for, LTA oxidation in 95% HOAc have been evaluated applying Kendall's treatment. The ρ^* value in PIA oxidation in 10% aq. HOAc on the basis of computed σ^* values and acid independent rate constant (k_i) is found to be -2.5. In 95% HOAc the plot of σ^* versus log k_i falls into two distinct lines with ρ^* values -2.5 and $+0.3$. Analogous plot for LTA oxidation gives ρ^* values of -2.0 and $+0.2$ respectively. The plot of log k_2 (PIA) versus log k_2 (LTA) is linear. A similarity in mechanism has been envisaged.

Kinetics of oxidation of amino acids by a variety of oxidants like Mn(III)[1], Co(III)[2], Ag(I)-catalysed peroxydisulphate[3], Os(VIII)-catalysed hexacyanoferrate(III)[4] and chloramine-T[5] have been reported. The present investigation deals with the oxidation of α-amino acids by phenyliodosyl acetate (PIA) and lead tetraacetate (LTA) in aqueous acetic acid (10%, 60%, 95%, v/v) in the presence of perchloric acid to see if there are any similarities in PIA and LTA oxidations.

Materials and Methods

Phenyliodosyl acetate was prepared according to the modified method of Boeseken and Schneider[6], m.p. 158°. Glycine, L-phenylalanine, L-leucine, L-valine and L-alanine (Loba) were used as such. Perchloric acid (E. Merck, GR) was standardised and measured volumes were taken from stock solution for each experiment. Self-decomposition of oxidants, in the solvent mixtures employed, was found to be negligible. Standard iodometric procedure was adopted[7,8] for the estimation of unreacted PIA and LTA. All the experiments were carried out in duplicate and the results are reproducible within ±3%.

The products of oxidation of glycine, L-phenylalanine, L-leucine, L-valine and L-alanine were formaldehyde, phenylacetaldehyde, isovaleraldehyde, isobutyraldehyde and acetaldehyde respectively and these were fully characterised by preparing their 2,4-dinitrophenylhydrazone derivatives and directly comparing (m.m.p.) these with the authentic specimens.

Results

PIA oxidation

The second order rate constants k_2 (dm^3 mol^{-1} s^{-1}) at varying [acid] are recorded in Table 1. Plots of log k_2 versus log $[H^+]$ yield unit negative slopes except for glycine for which the slope is -0.5.

Increasing the proportion of acetic acid in the reaction mixture retards the rate. In the presence of 0.02 mol dm^{-3} $HClO_4$ at 60° C the k_2 values in 60% HOAc are 0.0540, 0.0185, 0.0077 and 0.0078 dm^3 mol^{-1} s^{-1} for L-phenylalanine, L-leucine, L-valine and L-alanine respectively. The corresponding k_2 values in 95% HOAc are 0.0069, 0.0060, 0.0026 and 0.0022 dm^3

Table 1 —Effect of Varying the [Acid] on the Reaction Rate
[PIA] = 11.0×10^{-4} mol dm^{-3}; HOAc = 10% (v/v); temp. = 60°C

Substrate	$10^3 \times$ [S] (mol dm^{-3})	k_2 (dm^3 mol^{-1} s^{-1}) at $[H^+]$ (mol dm^3)			
		0.01	0.02	0.04	0.10
Glycine	10.0	0.0050	0.0029	0.0022	0.0016
L-Phenylalanine	2.50	0.5393	0.3000	0.1464	0.0396
L-Leucine	2.80	0.2519	0.1312	0.0459	0.0152
L-Valine	5.20	0.0775	0.0384	0.0138	0.0057
L-Alanine	5.20	0.1089	0.0458	0.0190	0.0054

mol^{-1} s^{-1}. However the plot of log k_2 versus $(D-1)/(2D+1)$ is not linear in the entire range of solvent composition. The effect of ionic strength is marginal. Added NaOAc accelerates the rate upto a concentration of 0.2 mol dm^{-3}, thereafter further variation in [NaOAc] has marginal effect. The k_2 values for glycine, L-phenylalanine, L-leucine, L-valine and L-alanine in 95% HOAc in the presence of 0.02 mol dm^{-3} of NaOAc are 0.0026, 0.0898, 0.0289, 0.0126 and 0.0153 dm^3 mol^{-1}, respectively. The activation parameters have been computed from the linear Arrhenius plots, the kinetic runs being carried out at 50°, 60° and 70° (Table 2).

Oxidation by LTA

Lead tetraacetate oxidation of these substrates also follows a second order kinetics. The k_2 values at 60° for glycine, L-phenylalanine, L-leucine, L-valine and L-alanine in 95% HOAc in the presence of 0.02 mol dm^{-3} $HClO_4$ are 0.0042, 0.0055, 0.0049, 0.0035 and 0.0031 dm^3 mol^{-1} s^{-1} respectively at [substrate] = 0.01 mol dm^{-3} and [LTA] = 0.0012 mol dm^{-3}. The k_2 values show inverse dependence on $[H^+]$. Added sodium acetate accelerates the rate. The k_2 values for the above substrates at 60° in 95% HOAc in the presence of 0.02 mol dm^{-3} NaOAc are 0.0233, 0.0699, 0.0361, 0.0155 and 0.0179 dm^3 mol^{-1} s^{-1} respectively. Rate constants at 60°, 70° and 80°C have been determined. The activation parameters are recorded in Table 3.

Discussion

The order of reactivities among the substrates is: L-phenylalanine > L-leucine > L-valine > L-alanine > glycine.

Table 2—Activation Parameters in PIA Oxidation of α-Amino Acids at 60°C

Substrate	E_a (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\log_{10}A$	$\Delta S^{\ddagger}$ (JK^{-1} mol^{-1})
Glycine	77.86	75.09	9.85	−65.94
L-Phenylalanine	86.47	83.70	13.25	−0.588
L-Leucine	98.40	95.63	13.78	+9.78
L-Valine	97.65	94.87	14.10	+10.96
L-Alanine	84.75	81.98	12.20	−20.91

Table 3—Activation Parameters in LTA Oxidation of α-Amino Acids at 60°C

Substrate	E_a (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\log_{10}A$	$-\Delta S^{\ddagger}$ (JK^{-1} mol^{-1})
Glycine	73.04	70.26	9.03	81.48
L-Phenylalanine	81.31	78.54	10.45	54.18
L-Leucine	69.84	67.07	8.60	89.75
L-Valine	81.52	78.75	10.30	57.66
L-Alanine	85.38	82.61	10.85	46.70

Thus the benzyl group in phenylalanine and $(CH_3)_2CHCH_2$ group in leucine act as strongly electron-releasing groups. As such the usual Taft σ^* values of these groups do not reflect on the rates of oxidation of phenylalanine and leucine so also the steric substituent constants of these groups. Hence the electron-releasing nature, rather than the inductive effect of these polar groups appears to control the reactivity. Electron-releasing power of a phenyl group is twice that of a *p*-methyl group in aromatic substitution. Rocek[9] while studying the Cr(VI) oxidation of primary alcohols found that the maximum increment for a methylene group is −0.1. As such the computed σ^* value for the benzyl group would be $-0.34+(-0.1)=-0.44$. The σ^* value[10] of $(CH_3)_2CH$ is −0.19. Hence the computed σ^*-value for $(CH_3)_2CHCH_2$ is −0.29. Further, to correlate the values with substrate structure, one has to evaluate the acid-independent rate constants since the pK_a values of the conjugate acids of these substrates are not identical. This can be done by applying the Kendall's treatment[11] using Eq. (1),

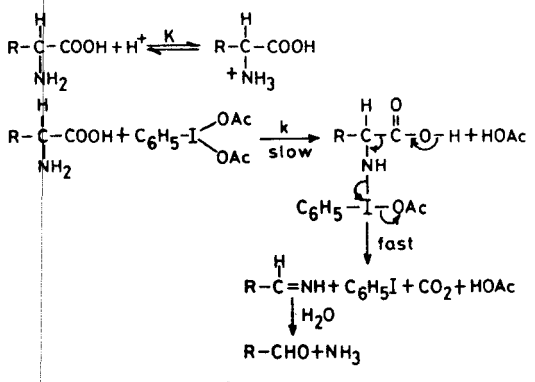
$$\log[B] = H_o - pK_a + \log[BH^+] \qquad \ldots(1)$$

where [B] is the free base concentration, H_o stands for the Hammett acidity function, pK_a relates to the dissociation constant of the conjugate acid of the base and $[BH^+]$ is the concentration of the protonated base which may be approximated to the stoichiometric concentration. Thus the pseudo-first order rate constant, k_1 (s^{-1}) when divided by the free [base] would give the acid-independent rate constant, k_i(dm^3 mol^{-1} s^{-1}) to a reasonable approximation. The computed k_i values in PIA oxidation of glycine, L-phenylalanine, L-leucine, L-valine and L-alanine are 0.0157, 2.963, 0.7747, 0.2184 and 0.2863 in 10% HOAc and 0.2966, 2.720, 1.364, 0.5266 and 0.5663 in 95% HOAc respectively. The corresponding values for LTA oxidation in 95% HOAc are 0.9800, 2.226, 1.105, 0.7120 and 0.8389. The plot of log k_i versus σ^*-values for PIA oxidation in 10% aq. HOAc is linear with a $\rho^* = -2.5$. The corresponding plots in 95% HOAc for PIA and LTA oxidations show distinct breaks with ρ^*-values of −2.5 and −2.0 for substrates with electron-releasing groups and ρ^*-values of −0.3 and +0.2 for substrates with electron-withdrawing groups. This shows that the LTA and PIA oxidations of these substrates proceed through a similar mechanism. The plots of log k_2 (PIA oxidation) against log k_2 (LTA oxidation) in 95% HOAc in the presence of 0.02 mol dm^{-3} $HClO_4$ and in 95% HOAc in the presence of 0.02 mol dm^{-3} $HClO_4$ and in 95% HOAc in the presence of 0.02 mol dm^{-3} NaOAc are also fairly linear, further supporting the above assumption. A high negative ρ^*-value for electron-releasing groups point to a

transition state with cationic character while a low ρ^*-value for electron-withdrawing groups points to a radical process involving hydrogen atom transfer.

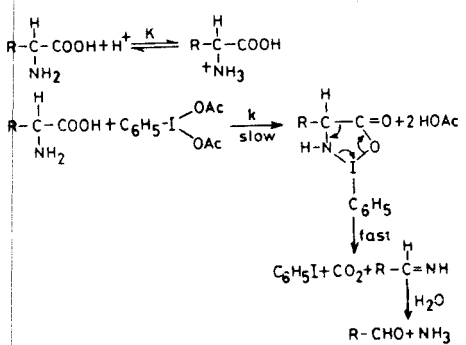
Mechanism

The kinetic results of the present study point to a transition state involving one molecule of the substrate and one molecule of the oxidant. The mechanism shown in Scheme 1 may be proposed for PIA oxidation of the α-amino acids.



Scheme 1

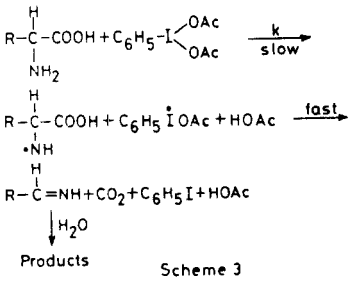
Alternatively one might envisage the formation of a cyclic ester as shown in Scheme 2.



Scheme 2

The extent of formation of this iodinium ester depends on the nature of the substituent R. For electron-releasing groups the electrophilic attack of PIA would be facilitated as these groups would stabilise the transition state by electron accession into the reaction site. However, for electron-withdrawing groups one might envisage a radical process (Scheme 3) on the basis of a low ρ^*-value.

The analogous transition state for LTA oxidation might envisage a cyclic Pb(IV) ester or a radical process involving OAc. However the radical mechanism seems



Scheme 3

to be the preferred one for substrates like glycine, in solvent medium containing high proportions of HOAc.

Rate law

The total [substrate] is given by,

$$[S]_T = [S] + [SH^+]$$
$$= [S] + K[H^+][S]$$

$$\text{or } [S] = \frac{[S]_T}{1 + K[H^+]}$$

The rate as expressed in terms of decrease in [PIA] is given by Eq. (2).

$$-\frac{d[PIA]}{dt} = k[S][PIA] = \frac{k[S]_T[PIA]}{1 + K[H^+]} \qquad \ldots(2)$$

This explains the inverse fractional dependence on $[H^+]$ for glycine when the second term in the denominator is comparable to unity. When K is large, the rate expression is given by Eq. (3).

$$-\frac{d[PIA]}{dt} = \frac{k}{K}[S]_T[PIA]/[H^+]$$
$$= k_2[S]_T[PIA]/[H^+] \qquad \ldots(3)$$

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