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Oxidation of Methionine by Tripropylammonium Fluorochromate-A Kinetic and Mechanistic Study

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Abstract: The kinetics of oxidation of methionine (Met) by tripropylammonium fluorochromate (TriPAFC) has been studied in the presence of chloroacetic acid in aqueous acetic acid medium. The reaction is first order with respect to methionine, TriPAFC and acid. The reaction rate has been determined at different temperatures and activation parameters calculated. With an increase in the amount of acetic acid in its aqueous mixture, the rate increases. The reaction does not induce polymerization of acrylonitrile. A suitable mechanism has been proposed.

Keywords: Tripropylammonium fluorochromate, Methionine, Kinetics, Oxidation, Mechanism

Introduction

Oxidation kinetics has received considerable attention due to the wide range of biological processes in which metal ions participate. Chromium(VI) acts as an efficient catalyst in redox reactions. The search for new oxidizing agents is of interest to synthetic organic chemists. Many such reagents have been developed in recent years with some success. In recent years, significant improvements were achieved by the use of new oxidizing agents such as benzimidazolium fluorochromate[1], *N*-methyl benzylammonium fluorochromate[2], tributylammonium chlorochromate[3], pyridinium fluorochromate[4], imidazolium dichromate[5] and isoquinolinium bromochromate[6] for the study of the kinetics and mechanism of various organic compounds.

Extensive studies on the mechanism of oxidation of methionine by several oxidants have been reported[7-9]. Methionine is an intermediate in the biosynthesis of cysteine, carnitine, taurine, lecithin, phosphatidylcholine and other phospholipids. It is a naturally occurring sulphur containing amino acid, has three coordination sites: at the N, O and S centers. Sulphur has been established as the most susceptible to attack by chromium(VI)[10-12], where the formation of an intermediate (chromate ester) provides a low energy path for electron transfer. Methionine is a methyl door and this process in the body is activated by adenosine triphosphate (ATP) and a liver enzyme such as phosphatase or dehydrogenase[13]. Oxidation of methionine by chromium(VI) has been investigated by a number of workers[14-16].

Literature survey reveals that no report is available on the kinetics of oxidation of methionine by TriPAFC. In this article, the kinetics and mechanism of the oxidation of methionine by TriPAFC in aqueous acetic acid mixture are reported, with the view to understand the utility of solvent variation studies in the understanding of the mechanism of this biologically important amino acid because it may reveal the mechanism of amino acid metabolism.

Experimental

Tripropylammine and chromium trioxide were obtained from Fluka (Buchs, Switzerland). DL-methionine (E Merck, Germany) was used as received. Acetic acid was purified by standard method[17] and the fraction distilling at 118 °C was collected. All other chemicals used were of AnalaR grade.

Preparation of tripropylammonium fluorochromate

Tripropylammonium fluorochromate was easily prepared as follows: Chromium(VI) oxide (15.0 g, 0.150 mol) was dissolved in water in a polyethylene beaker and 40% hydrofluoric acid (11.3 mL, 0.225 mol) was added with stirring at 0 °C. To the resultant orange solution, tripropylammine (28.3 mL, 0.150 mol) was added drop wise with stirring to this solution over a period of 0.5 h and stirring was continued for 0.5 h at 0 °C. The precipitated orange solid was isolated by filtration, washed with petroleum ether (3x60 mL) and dried in vacuum for 2 h at room temperature[18]. Yield 37.5 g (95%); mp 142 °C.

$$\underset{\text{Tripropylamine}}{N(C_3H_7)_3} \xrightarrow[0\ ^oC]{CrO_3\ /\ 40\%\ HF} \underset{\text{Tripropylammonium flourochromate}}{(C_3H_7)_3NH^+[CrO_3F]^-} \qquad (1)$$

The bright orange crystalline reagent was stored in polyethylene containers for long periods without decomposition. The chromium(VI) content was easily determined iodometrically. Tripropylammonium fluorochromate was soluble in water, dimethylformamide, acetonitrile, acetone and dichloromethane and was sparingly soluble in benzene, carbon tetrachloride, chloroform and hexane.

Stoichiometric analysis and product study

The stoichiometry of the reaction was determined by performing the several sets of experiments with varying amounts of TriPAFC largely in excess over methionine. The disappearance of TriPAFC was monitored until constant titre values were obtained.

$$Me - S - R + O_2CrFO^-TriPNH^+ \rightarrow \quad Me - SO - R + OCrFO^-\ TriPNH^+ \qquad (2)$$
$$(R = -CH_2CH_2CH(NH_2)COOH)$$

The reaction mixture was allowed to stand for a few hours. Then, sodium bicarbonate was added and stirred vigorously, followed by drop wise addition of benzoyl chloride solution. The precipitate *N* - benzoyl methionine sulphoxide was confirmed[19] by its m.p 183 °C. The procedure is similar to the one employed in the oxidation of *L*–methionine[20] by chromium(VI). Acetone-ethanol mixture (1:1) added to the reaction mixture resulted in the precipitate of methionine sulphoxide, which was identified [21] by its m.p 238 °C.

Kinetic measurement

The pseudo-first-order conditions were attained by maintaining a large excess (x 15 or more) of methionine over TriPAFC. The reactions were carried out in aqueous acetic acid medium in the presence of chloroacetic acid. The studies were carried out in the temperature range of

298 – 313 K. All the solutions were kept in a thermostat at constant temperature which was controlled using a thermostat of ±0.1 ^{o}C accuracy. The required volumes of these solutions for each run were mixed and 2 mL aliquots of the reaction mixture were pipetted out at convenient time intervals and quenched in 10 mL 2% KI solution and the liberated iodine was titrated against thiosulphate using starch as indicator. The pseudo-first-order rate constants were evaluated from log titre *versus* time plots. All the rate constants reported are in an average of two or more determinations. The second order rate constant k_2, was obtained from the relation $k_2 = k_{obs}$ / [Met].

Data analysis

Data analysis were performed using microcal origin (version 6.0) computer software. The goodness of the fit is discussed using the correlation coefficients and standard deviations.

Results and Discussion

Order of reaction

The oxidation of methionine with TriPAFC in aqueous acetic acid medium in the presence of chloroacetic acid yields sulphoxide. The rate of oxidation was found to be first order in [Met]. Linear plots of log k_1 *versus* log [Met] with unit slope demonstrate the first-order dependence of the rate on [Met]. The near constancy in the values of k_1 irrespective of the concentration of the TriPAFC confirms the first order dependence on TriPAFC (Table 1).

The dependence of the reaction rate on the hydrogen ion concentration has been investigated at different initial concentrations of chloroacetic acid while keeping the concentrations of the other reactants constant. It may be seen that the rate of reaction increases linearly with an increase in the hydrogen ion concentration (Table 1). A plot of log k_1 *versus* log [H^+] is linear with a unit slope. The reaction proceeds completely through an acid-caalysed pathway [22]. The acid catalysis may well be attributed to the protonated ion on TriPAFC to give a stronger oxidant and electrophile. Therefore the rate law can be represented as:

$$- d[\text{TriPAFC}] / dt = k [\text{Met}] [\text{TriPAFC}] [H^+]$$

Table 1. Effect of varying the concentration of [Met], [TriPAFC] and [H^+] on the rate of reaction at 303 K, Solvent composition = 30% AcOH - 70% H_2O (v/v)

10^3[TriPAFC] mol.dm^{-3}	10^2 [Met] mol.dm^{-3}	[H^+] mol.dm^{-3}	$10^4 k_1$ s^{-1}
0.5	2.0	0.32	5.56 ± 0.10
1.0	2.0	0.32	5.52 ± 0.08
1.5	2.0	0.32	5.48 ± 0.16
2.0	2.0	0.32	5.58 ± 0.04
2.5	2.0	0.32	5.50 ± 0.06
1.0	2.0	0.32	5.52 ± 0.08
1.0	1.5	0.32	4.08 ± 0.08
1.0	2.5	0.32	6.82 ± 0.12
1.0	3.0	0.32	8.22 ± 0.12
1.0	2.0	0.16	2.72 ± 0.8
1.0	2.0	0.48	8.18 ± 0.10
1.0	2.0	0.64	11.00 ± 0.12
1.0	2.0	0.80	13.68 ± 0.14
1.0	2.0	0.32	4.84± 0.04[a]
1.0	2.0	0.32	2.64± 0.05[b]

[a] *Contained 0.001 mol dm^{-3} acrylonitrile.* [b] *In the presence of 0.003 mol dm^{-3} Mn (II)*

Induced polymerisation

The oxidation of Met in an atmosphere of nitrogen failed to induce the polymerization of acrylonitrile. Furthermore, the rate of oxidation decreased with the addition of Mn(II) (Table 1). Therefore, a one-electron oxidation giving rise to free radicals is unlikely.

Effect of solvent composition

The effect from solvent composition on the reaction rate was studied by varying the concentration of acetic acid from 30% to 70%. The reaction rate is increases markedly with the increase in the proportion of acetic acid in the medium (Table 2). When the acid content increases in the medium, the acidity of the medium is increased whereas the dielectric constant of the medium is decreased. These two effects cause the rate of the oxidation to increase markedly. The enhancement of the reaction rate with an increase in the amount of acetic acid generally may be attributed to two factors, *viz,* (i) the increase in acidity occurring at constant $[H^+]$ and (ii) the decrease in the dielectric constant with an increase in the acetic acid content. The plots of log k_1 against the inverse of the dielectric constant are linear with positive slopes, indicating that an interaction between a positive ion and a dipolar molecule[23].

Table 2. Effect of varying solvent polarity on the rate of reaction at 303 K [Met] = 2.0×10^{-2} mol.dm^{-3}; [TriPAFC] = 1.0×10^{-3} mol.dm^{-3} ; $[H^+]$ = 0.32 mol.dm^{-3}

%Water	%Acetic acid	Dielectric constant	$10^4 k_1$ s^{-1}
70	30	72.0	5.52 ± 0.08
60	40	63.3	6.52 ± 0.04
50	50	56.0	7.76 ± 0.12
40	60	45.5	8.60 ± 0.06
30	70	38.5	9.84 ± 0.11

Mechanism of oxidation

Based on the above kinetic observations, *i.e.* first order dependence on [Met], [TriPAFC] and $[H^+]$, the following mechanism is proposed. Under the present experimental conditions, methionine is oxidized to the sulphoxide stage only. The linear increase in the rate with acidity suggests the involvement of protonated TriPAFC in the rate determining step. In the first step TriPAFC becomes protonated. The protonated TriPAFC attacks the substrate, in a slow step, to form a complex, which subsequently decomposes to give the products in a fast step. The proposed scheme envisages an oxygen atom transfer from the oxidant and that is in agreement with the earlier observations. The electrophile attack on the sulphide - sulphur can be viewed as an S_N2 reaction[14].

Rate law

The above mechanism leads to the following rate law:

Rate	=	k_3 [Complex]
[Complex]	=	k_2 [Met] [TriPAFCH$^+$]
[TriPAFCH$^+$]	=	k_1[TriPAFC][H$^+$]
[Complex]	=	$k_1k_2k_3$[Met][TriPAFC][H$^+$]
– d[TriPAFC] / dt	=	$k_1k_2k_3$ [Met] [TriPAFC] [H$^+$]

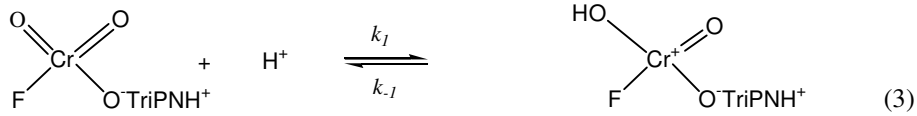
The rate law in its final form accounts for the observed kinetics. The negative entropy of activation suggests complex formation in the transition state. The linear increase in rate with acidity suggests the involvement of protonated TriPAFC in the rate-determining step.

Thermodynamic parameters

The kinetics of oxidation of methionine was studied at four different temperatures *viz*., 298, 303, 308 and 313 K in acetic acid - water medium in presence of chloroacetic acid. The second order rate constants were calculated (Table 3). The Arrhenius plot of log k_2 *versus* 1/T is found to be linear. The enthalpy of activation, entropy of activation and free energy of activation were calculated from k_2 at 298, 303, 308 and 313 K using the eyring relationship by the method of least square and presented in Table 3. The least square method gives the values and standard errors of enthalpy and entropy of activation respectively. Statistical analysis of the Eyring equation clearly confirms that the standard errors of $\Delta H^{\#}$ and $\Delta S^{\#}$ correlate[24]. The entropy of activation is negative for methionine. The negative entropy of activation in conjunction with other experimental data supports the mechanism outlined in (Scheme 1).

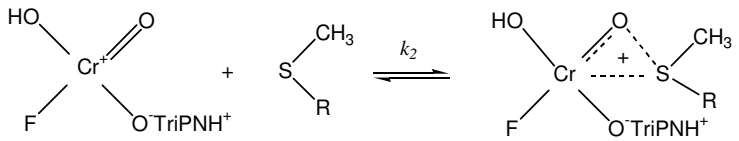
Table 3. Activation parameters and second order rate constants for the oxidation of methionine by TriPAFC [Met] = 2.0×10^{-2} M; [TriPAFC] = 1.0×10^{-3} M; $[H^+]$ = 0.32 M Solvent composition = 30% AcOH- 70% H_2O (v/v)

Substrate	$10^2 \times k_2$,				E_a	$\Delta H^{\#}$	$-\Delta S^{\#}$	$\Delta G^{\#}$ kJmol^{-1}
	298K	303K	308K	313K	kJmol^{-1}	kJmol^{-1}	$JK^{-1}_{1}mol^{-}$	(at 303K)
Methionine	1.74± 0.12	2.76± 0.04	4.16± 0.06	6.16± 0.10	65.2± 0.9	62.6± 0.7	68.2± 2.0	4 83.3± 1.4



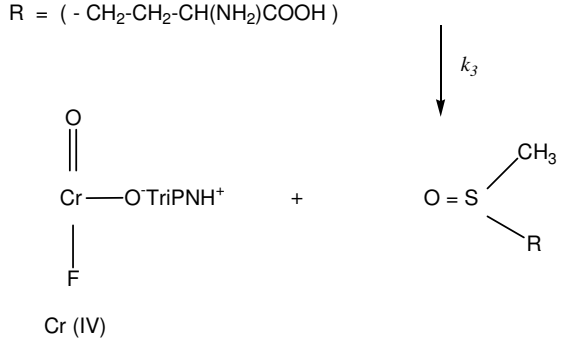
(3)

$TriPNH^+ = (C_3H_7)_3NH^+$



(4)

R = (- CH_2-CH_2-CH(NH_2)COOH)



(5)

Cr (IV)

Scheme 1

Conclusion

In conclusion the oxidation of methionine by TriPAFC is first order with respect to [Met], [TriPAFC] and [H^+]. Methionine is oxidized to sulphoxide stage only. The entropy of activation is negative, suggesting the formation of a complex in a rate-determining step.

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