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Oxidation Kinetics of DL-Methionine, a Sulphur containing Amino acid by Tripropylammonium Chlorochromate

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Abstract: The oxidation of methionine (Met) by tripropylammonium chlororochromate (TPACC) in dimethylsulphoxide (DMSO) leads to the formation of corresponding sulphoxide. The reaction is of first order with respect to TPACC. Michaelis-Menten type kinetics was observed with respect to methionine. The reaction is catalysed by hydrogen ions. The hydrogen-ion dependence has the form: k_{obs} = a + b [H^+]. The oxidation of methionine was studied in nineteen different organic solvents. The solvent effect was analyzed by Kamlet's and Swain's multiparametric equations. Solvent effect indicated the importance of the cation-solvating power of the solvent. A suitable mechanism has also been postulated.

Keywords: Halochromate, Kinetics, Mechanism, Methionine, Oxidation.

1.INTRODUCTION

Cr(VI) salts of have long been used as oxidizing reagents in synthetic organic chemistry. However these salts are rather drastic in nature and non-selective oxidants. Further, they are insoluble in most of the organic solvents. Thus miscibility is a problem. To overcome these limitations, a large number of organic derivatives of Cr(VI) have been prepared and used in organic synthesis as mild and selective oxidants in non-aqueous solvents[1]. One of such compounds is tripropylammonium chlorochromate (TPACC) reported by Firozabadi *et al.*[2]. We have been interested in the kinetic and mechanistic aspects of the oxidation by complex salts of Cr(VI) and several studies have already been

reported from our laboratory[3-6]. It is, known however, that mode of oxidation depends upon the nature of counter-ion attached to the chromium anion. Methionine (Met), a sulphur-containing essential amino acid, is reported to behave differently from other amino acids, towards many oxidants[7,8], due to electron-rich sulphur center which is easily oxidizable. There seems to be no report on the oxidation aspects of TPACC. Therefore, in continuation of our earlier work by halochromates, we report here the kinetics of oxidation of DL-methionine by TPACC in dimethylsulphoxide (DMSO) as solvent. A suitable mechanism has also been proposed.

2.EXPERIMENTAL

2.1. Materials: TPACC was prepared by the reported method[2] and its purity checked by an iodometric method. Methionime (Merck) was used as supplied. Due to non-aqueous nature of the solvent, toluene-*p*-sulphonic acid (TsOH) was used as a source of hydrogen ions. Other solvents were purified by the usual methods[9].

2.2. Product Analysis: Product analysis was carried out under kinetic conditions. The oxidation of Met by TPACC resulted in the formation of corresponding sulphoxide, which was determined by the reported method[10]. The yield of sulphoxide was 94±3%. The oxidation state of chromium in completely reduced reaction mixtures, as determined iodometrically, was +4.

2.3. Kinetic measurements: The pseudo-first order conditions were attained by maintaining a large excess (× 15 or more) of the Met over TPACC. The solvent was DMSO, unless specified otherwise. The reactions were followed, at constant temperatures (±0.1 K), by monitoring the decrease in [TPACC] spectrophotometrically at 370 nm. No other reactant or product has any significant absorption at this wavelength. The pseudo-first order rate constant, k_{obs}, was evaluated from the linear (r = 0.990 - 0.999) plots of log [TPACC] against time for up to 80% reaction. Duplicate kinetic runs showed that the rate constants were reproducible to within±3%. All experiments, other than those for studying the effect of hydrogen ions, were carried out in the absence of TsOH. The second order rate constant, k_2, was evaluated from the relation $k_2 = k_{obs}/[Met]$. Simple and multivariate linear regression analyses were carried out by the least-squares method on a personal computer.

3.RESULTS AND DISCUSSION

3.1. Stoichiometry: The oxidation of methionine by TPACC resulted in the formation of the corresponding sulfoxides. The overall reaction may therefore, be represented as equation (1).

$$Me - S - R + CrO_2Cl\ O^-N^+H(C_3H_7)_3 \longrightarrow Me - \underset{\underset{O}{||}}{S} - R + CrOCl\ O^-N^+H(C_3H_7)_3 \qquad (1)$$

Where R is $CH_2CH_2CH(NH_2)\ COOH$

TPACC undergoes a two-electron change. This is in accord with the earlier observations with structurally similar halochromates. It has already been shown that both PFC[11] and PCC[12] act as two electron oxidants and are reduced to chromium (IV) species by determining the oxidation state of chromium by magnetic susceptibility, ESR and IR studies.

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3.2.Rate Laws: The reactions were found to be first order with respect to TPACC (Figure 1). In individual kinetic runs, plots of log [TPACC] *versus* time were linear (r^2> 0.995). Further, it was found that the observed rate constant, k_{obs}, does not depend on the initial concentration of TPACC. The order with respect to methionine was less than one **(Table 1)**. A plot of $1/k_{obs}$*versus* 1/[Met] was linear with an intercept on the rate ordinate **(Figure 2)**. Thus Michaelis-Menten type kinetics were observed with respect to Met. This leads to the postulation of following overall mechanism (equations 2 and 3) and the rate law (4).

Table – 1: Rate Constants for the Oxidation of Methionine by TPACC at 298 K

10^3 [TPACC] (mol dm^{-3})	[Met] (mol dm^{-3})	[TsOH] (mol dm^{-3})	$10^4 k_{obs}$ (mol dm^{-3})
1.0	0.10	0.00	6.84
1.0	0.20	0.00	9.99
1.0	0.40	0.00	13.5
1.0	0.60	0.00	15.3
1.0	0.80	0.00	16.0
1.0	1.00	0.00	17.1
1.0	1.50	0.00	18.0
1.0	3.00	0.00	18.9
2.0	0.40	0.00	13.8
4.0	0.40	0.00	12.6
6.0	0.40	0.00	13.0
8.0	0.40	0.00	13.7
1.0	0.20	0.00	10.8*
[a] contained 0.001 M acrylonitrile			

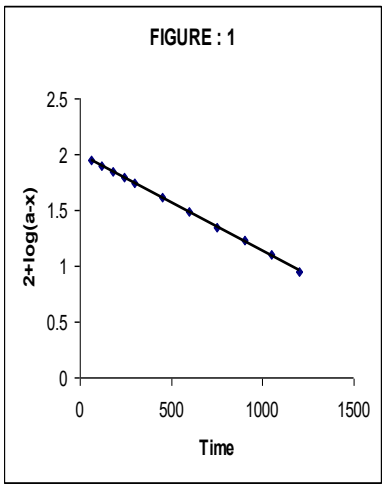

Figure 1.: Oxidation of MET by TPACC: A typical Kinetic Run

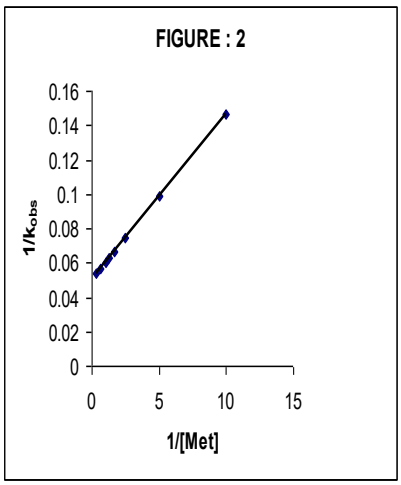

Figure 2 Oxidation of MET by TPACC: A double reciprocal plot

$$\text{Met} + \text{TPACC} \underset{}{\overset{K}{\leftrightarrows}} [\text{Complex}] \qquad (2)$$

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$$[\text{Complex}] \xrightarrow{k_2} \text{Products} \quad (3)$$

$$\text{Rate} = k_2 K [\text{Met}] [\text{TPACC}] / (1 + K [\text{Met}]) \quad (4)$$

The dependence of k_{obs} on the concentration of methionine was studied at different temperatures and the values of K and k_2 were evaluated from the double reciprocal plots. The thermodynamic parameters for the complex formation and activation parameters of the disproportionation of the complexes, at 298 K, were calculated from the values of K and k_2 respectively at different temperatures **(Tables 2 and 3).**

Table – 2: Formation Constants and Thermodynamic Parameters of the Oxidation of TPACC-Methionine Complexes

K / (dm^3 mol^{-1})				$-\Delta H^*$	$-\Delta S^*$	$-\Delta G^*$
288K	298K	308K	318K	(kJ mol^{-1})	(J mol^1 K^{-1})	(kJ mol^{-1})
6.03	5.22	4.38	3.69	15.7±0.6	31±2	6.55±0.5

Table – 3: Rate Constants and Activation Parameters of the Decomposition of TPACC – Methionine Complexes

$10^4 k_2$ / (dm^3 mol^{-1}s^{-1})				$\Delta H^*-\Delta S^*$	ΔG^*
288K	298K	308K	318K	(kJ mol^{-1})	(J mol^1 K^{-1})	(kJ mol^{-1})
8.82	20.0	43.2	91.8	57.1±0.6	108±2	88.2±0.5

3.3.Induced Polymerization of Acrylonitrile/ test for free radicals: The oxidation of Met, in an atmosphere of nitrogen, failed to induce the polymerization of acrylonitrile. Further, the addition of acrylonitrile had no effect on the rate of oxidation **(Table 1).** Therefore, a one-electron oxidation, giving rise to free radicals, is unlikely. To further confirm the absence of free radicals in the reaction pathway, the reaction was carried out in the presence of 0.05 mol dm^{-3} of 2,6-di-t-butyl-4-methylphenol (butylated hydroxytoluene or BHT). It was observed that BHT was recovered unchanged, almost quantitatively.

3.4. Effect of acidity: The reaction was studied at different acidities by adding varying amount of toluene-p-sulphonic acid (TsOH) to the reaction mixtures. The reaction is catalyzed by hydrogen ions (**Table 4).** The hydrogen-ion dependence has the form $k_{obs} = a + b [H^+]$. The values of *a* and *b* are

$6.86\pm0.21\times10^{-4}$ s^{-1} and $12.4\pm0.35\times10^{-4}$ mol^{-1} dm^3 s^{-1} respectively (r^2 = 0.9968).

Table – 4: Dependence of the Reaction Rate on Hydrogen-ion Concentration

[TPACC] = 0.001 mol dm^{-3};	[Met] = 1.0 mol dm^{-3};			Temp. = 298 K		
$[H^+]$/mol dm^{-3}	0.10	0.20	0.40	0.60	0.80	1.00
Met	8.17	10.2	11.7	15.0	17.1	19.1

3.5. Effect of Solvents: The oxidation of methionine was studied in 19 different organic solvents. The choice of solvent was limited due to the solubility of TPACC and its reaction with primary and secondary alcohols. There was no reaction with the solvents chosen. The kinetics were similar in all the solvents. The values of K and k_2 are recorded in Table 5.

Table – 5: Effect of Solvents on the oxidation of Methionine by TPACC at 298 K

Solvents	K (dm^{-3} mol^{-1})	10^5 k_{obs} (s^{-1})	Solvents	K (dm^{-3} mol^{-1})	10^5 k_{obs} (s^{-1})
Chloroform	5.58	75.6	Toluene	6.10	14.4
1,2-Dichloroethane	6.30	67.5	Acetophenone	5.58	70.2
Dichloromethane	5.49	63.0	THF	6.03	27.9
DMSO	5.25	198	t-Butylalcohol	6.31	33.3
Acetone	5.67	5.22	1,4-Dioxane	5.98	30.6
DMF	6.12	93.6	1,2-Dimethoxyethane	5.95	17.1
Butanone	6.03	41.4	CS_2	5.76	7.74
Nitrobenzene	5.94	77.4	Acetic Acid	6.04	33.9
Benzene	5.76	19.8	Ethyl Acetate	5.89	20.7
Cyclohexane	6.00	1.89			

3.6. Solvent Effect: The oxidation of Met was studied in nineteen organic solvents. The choice of solvents was limited due to the solubility of TPACC and its reaction with primary and secondary alcohols. There was no reaction with the chosen solvents. The kinetics are similar in the all the solvents. The values of K and k_2 are recorded in Table 5. A perusal of the data shows that the formation constants do not vary much with the nature of the solvents. However, the rate constants, k_2 varied considerably with the solvents. The rate constants for oxidation, k_2, in eighteen solvents (CS_2 was not considered, as the complete range of the solvent parameters was not available) were correlated in terms of the linear solvation energy relationship equation (6) of Kamlet *et al.*[13]

$$\log k_2 = A_0 + p\pi^* + b\beta + a\alpha \qquad (6)$$

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In this equation, π^* represents the solvent polarity, β the hydrogen bond acceptor basicities and α is the hydrogen bond donor acidity. A_0 is the intercept term. It may be mentioned here that out of the 18 solvents, 12 have a value of zero for α. The results of correlation analyses in terms of equation (6), a biparametric equation involving π^* and β, and separately with π^* and β are given below.

$$\log k_2 = -4.36 + 1.70\ (\pm 0.18)\ \pi^* + 0.13\ (\pm 0.15)\ \beta + 0.31\ (\pm 0.14)\ \alpha \quad (7)$$

$R^2 = 0.8792;\ \ sd = 0.17;\ \ n = 18;\ \ \psi = 0.38$

$$\log k_2 = -4.44 + 1.59\ (\pm 0.19)\ \pi^* + 0.24\ (\pm 0.16)\ \beta \quad (8)$$

$R^2 = 0.8392;\ \ sd = 0.19;\ \ n = 18;\ \ \psi = 0.43$

$$\log k_2 = -4.51 + 1.65\ (\pm 0.20)\ \pi^* \quad (9)$$

$r^2 = 0.8158;\ \ sd = 0.19;\ \ n = 18;\ \ \psi = 0.44$

$$\log k_2 = -2.63 + 0.52\ (\pm 0.35)\ \beta \quad (10)$$

$r^2 = 0.1199;\ \ sd = 0.42;\ \ n = 18;\ \ \psi = 0.97$

Here n is the number of data points and ψ is the Exner's statistical parameter.[14]

Kamlet's[13] triparametric equation explains *ca.* 89% of the effect of solvent on the oxidation. However, by Exner's[14] criterion the correlation is not even satisfactory (*cf.* eqn. 7). The major contribution is of solvent polarity. It alone accounted for *ca.* 88% of the data. Both β and α play relatively minor roles.

The data on the solvent effect were analysed in terms of Swain's equation[15] of cation- and anion-solvating concept of the solvents as well.

$$\log k_2 = aA + bB + C \quad (11)$$

Here A represents the anion-solvating power of the solvent and B the cation- solvating power. C is the intercept term. (A + B) is postulated to represent the solvent polarity. The rates in different solvents were analysed in terms of equation (11), separately with A and B and with (A + B).

$$\log k_2 = 1.25\ (\pm 0.03)\ A + 1.57\ (\pm 0.02)\ B - 3.84 \quad (12)$$

$R^2 = 0.9975;\ sd = 0.02;\ n = 19;\ \psi = 0.05$

$$\log k_2 = 1.03\ (\pm 0.52)\ A - 2.76 \quad (13)$$

$r^2 = 0.1885;\ sd = 0.42;\ n = 19;\ \psi = 0.93$

$$\log k_2 = 1.48\ (\pm 0.22)\ B - 3.43 \quad (14)$$

$r^2 = 0.7241;\ sd = 0.25;\ n = 19;\ \psi = 0.54$

$$\log k_2 = 1.47 \pm 0.04\ (A + B) - 3.83 \quad (15)$$

$r^2 = 0.9847;\ sd = 0.06;\ n = 19;\ \psi = 0.13$

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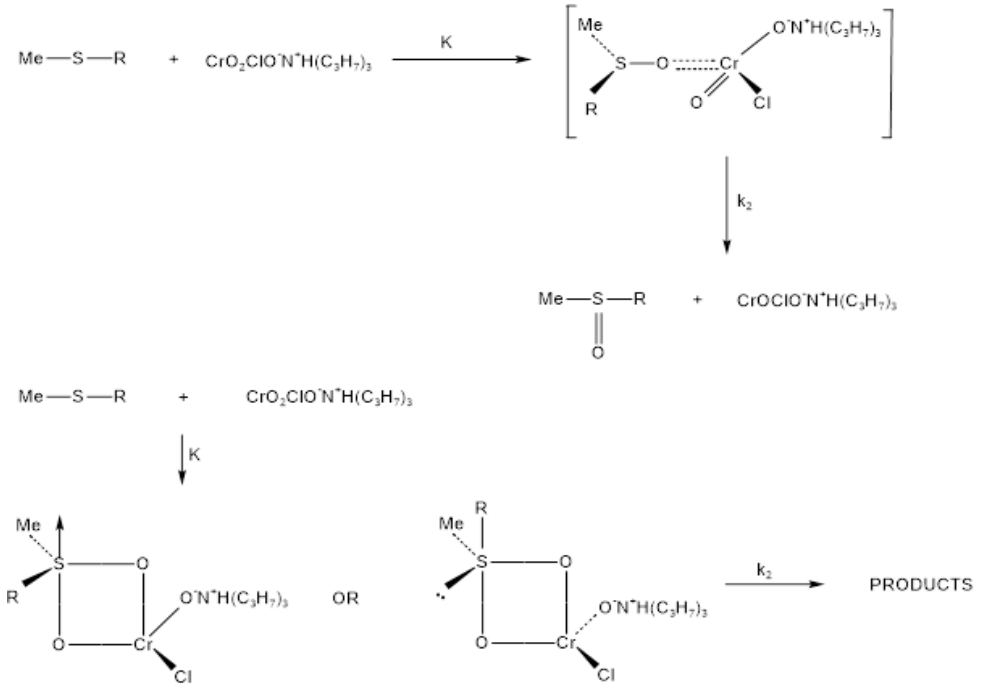
The rates of oxidation of methionine in different solvents show an excellent correlation with Swain's equation with both the cation- and anion- solvating powers playing significant roles, though the contribution of the cation-solvation is slightly more than that of the anion-solvation. The solvent polarity, represented by (A + B), also accounted for *ca.* 98% of the data. However, the correlations individually with A and B were poor. In view of the fact that solvent polarity is able to account for *ca.* 98% of the data, an attempt was made to correlate the rate with the relative permittivity of the solvent. However, a plot of log k_2 against the inverse of the relative permittivity is not linear ($r^2 = 0.4797$; sd = 0.34; $\psi = 0.74$).

The observed solvent effect points to a transition state more polar than the reactant state. Further, the formation of a dipolar transition state, similar to those of S_N2 reactions, is indicated by the major role of both anion- and cation-solvating powers. However, the solvent effect may also be explained assuming that the oxidant and the intermediate complex exist as ion-pair in non-polar solvent like cyclohexane and be considerably dissociated in more polar solvents.

4.MECHANISM

In view of the absence of any effect of radical scavenger, acrylonitrile, on the reaction rate and recovery of unchanged BHT, it is unlikely that a one-electron oxidation giving rise to free radicals, is operative in this oxidation reaction. The observed Michaelis – Menten type of kinetics observed with respect to methionine, suggests the formation of 1:1 complex of TPACC and Met in a rapid pre-equilibrium. With present set of data, it is difficult to state the definite nature of the intermediate complex. The experimental results can be accounted for in terms of electrophilic attack of methionine-sulphur at the metal *via* an intermediate complex. Transfer of an unshared pair of electrons to an empty d orbital of the metal resulted in the formation of a coordinate bond. The formation of intermediate is likely to undergo a further rapid reaction in which the incipient.



It is of interest to compare here the mode of oxidation of methionine by PFC,[16] pyridinium chlorochromate (PCC),[17] pyridinium bromochromate (PBC)[18] and TPACC. The oxidation by PFC and PBC presented a similar kinetic picture, i.e. the reactions are of first order with respect to the reductants. While in the oxidation by PCC and TPACC, Michaelis-Menten type kinetics was observed with respect to the reductants. It is possible that the values of the formation constants for the reductant-PFC/PBC complexes are very low. This resulted in the observation of second-order kinetics. No explanation of the difference is available presently. Solvent effects and the dependence of the hydrogen ions are of similar nature in all these reactions, for which essentially similar mechanisms have been proposed.

CONCLUSION

The oxidation of DL-methionine involves a rate-determining electrophilic attack of methionine sulfur at the metal ion *via* an intermediate complex. Both deprotonated and protonated forms of TPACC are reactive oxidizing species

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