

Kinetics and Mechanism of Oxidation of Methionine by Chromium(VI): Edta Catalysis

Subbiah Meenakshisundaram* and Rajagopal Vinothini

Department of Chemistry, Annamalai University, Annamalainagar – 608 002, India

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The kinetics of the oxidation of DL-methionine to sulfoxide by Cr^{VI} has been studied in aqueous acetic acid in the presence of sodium salt of ethylenediaminetetraacetic acid (edta). It appears that Cr^{VI}-edta is the active electrophile. The low dielectric constant of the medium favours the reactivity. Ionic strength and Mn^{II} have no significant effect on the conversion. The ratio $k(\text{D}_2\text{O}) / k(\text{H}_2\text{O}) \approx 1$ does not seem to indicate any significant solvent isotope effect. Highly negative ΔS^\ddagger values indicate a structured transition state. A ternary intermediate has been envisaged for describing the enhanced reactivity.

INTRODUCTION

Extensive studies on the mechanism of oxidation of methionine by several oxidants have been reported. Even though methionine, a naturally occurring sulfur containing amino acid, has three coordinating centres, *viz.*, O, N and S, it has been reported by McAuley and coworkers^{1–3} that the sulfur is more susceptible to attack by Cr^{VI}. Methionine is a methyl donor and this process in the body is activated by adenosine triphosphate (atp) and a liver enzyme such as phosphatase or dehydrogenase.⁴ Active methionine can transfer its methyl group to a variety of compounds and the high energy *S*-methyl bond is the prime reason for this behaviour. The oxidation of this biologically important amino acid is very important because it may reveal the mechanism of amino acid metabolism. As a part of our investigation on the mechanistic aspects of the edta catalysed Cr^{VI} oxidations,⁵ we report the results of the edta catalysed reaction of DL-methionine by Cr^{VI}.

EXPERIMENTAL

Materials

Potassium dichromate (Merck) was used without further purification. The purity of the compound was checked by iodometric assay. Disodium salt of edta and DL-methionine (Merck) were used as received. Acetic acid was purified by a method similar to that of Weissberger.⁶ All the other chemicals used were of AnalaR grade.

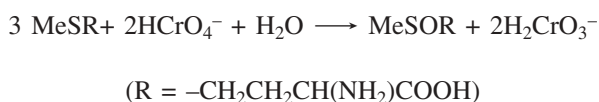
Kinetic Analysis

The reactions were carried out in aqueous acetic acid medium. The studies were carried out in the temperature range of 303–323 K. All the solutions were kept in a thermostat at constant temperature, which was controlled using a Gallenkemp thermostat of $\pm 0.1^\circ$ 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 thiosulfate to a starch end point. The pseudo-first-order rate constants were evaluated from log titre *versus* time plots. All the rate constants reported are an average of two or more determinations.

* Author to whom correspondence should be addressed. (E-mail: meenas1957@sify.com)

Stoichiometry and Product Analysis

The stoichiometry of the reaction was determined by performing the experiment at 303 K, under the conditions of $[\text{Cr}^{\text{VI}}] > [\text{methionine}]$. The disappearance of Cr^{VI} was monitored until constant titre values were obtained.



The reaction mixture was allowed to stand for a few hours. Then, sodium bicarbonate was added and stirred vigorously, followed by a dropwise addition of benzoyl chloride solution. The precipitate *N*-benzoyl methionine sulfoxide was confirmed by its m.p. 183 °C.⁷ The procedure is similar to the one employed in the oxidation of L-methionine by aqueous Cr^{VI} .⁸ Acetone-ethanol mixture (1:1) added to the reaction mixture resulted in the precipitate of methionine sulfoxide, which was identified by its m.p. 238 °C.⁹

RESULTS AND DISCUSSION

The reaction exhibits first-order dependence on the concentration of Cr^{VI} . The plots of log titre as a function of time were linear to at least 75 % completion of the reaction (Figure 1) ($r = 0.999$; $s = 0.015$). Evaluation of gradients of these lines gave the pseudo-first-order rate coefficients, k_{obs} . The reactivity decreased, as $[\text{Cr}^{\text{VI}}]$ increases as shown in Table I. Such observations in Cr^{VI} oxidations have been reported by several authors¹⁰⁻¹² and it was well explained by Wiberg.¹² As the Cr^{VI} concentration increased, a progressively smaller portion of the total amount was in the form of acid chromate ion and the rate constants decreased with the increasing Cr^{VI} concentration. Bakore *et al.*¹³ have established that HCrO_4^- is probably the active oxidising species and determined the concentration of HCrO_4^- from the gross concentration of Cr^{VI} and from the value of the equilibrium constant for the reaction.

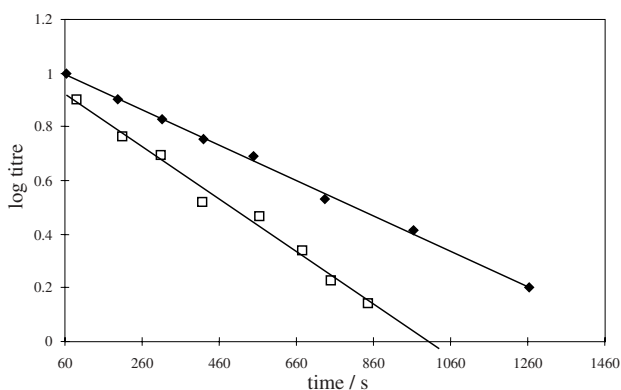


Figure 1: Pseudo-first-order plots for the edta catalysed oxidation of DL-methionine with $\text{K}_2\text{Cr}_2\text{O}_7$: 1.) $[\text{Oxidant}] = 3.7 \times 10^{-3} \text{ mol dm}^{-3}$, ◆; 2.) $[\text{Oxidant}] = 1.3 \times 10^{-3} \text{ mol dm}^{-3}$, □.

TABLE I. Effect of the oxidant (Cr^{VI}), substrate (DL-methionine) and edta concentrations on the reaction rate at 303 K in 30 % aqueous acetic acid

$10^3 [\text{Oxidant}]$ mol dm ⁻³	$10^2 [\text{Substrate}]$ mol dm ⁻³	$10^4 [\text{edta}]$ mol dm ⁻³	$10^4 k_{\text{obs}}$ s ⁻¹
1.2	5.0	5.0	21.72
2.5	5.0	5.0	16.58
3.7	5.0	5.0	15.16
5.0	5.0	5.0	9.36
5.0	0.6	5.0	4.25
5.0	1.2	5.0	6.15
5.0	2.5	5.0	7.08
5.0	3.7	5.0	8.26
5.0	5.0	2.5	6.59
5.0	5.0	10.0	14.53
5.0	5.0	15.0	18.93

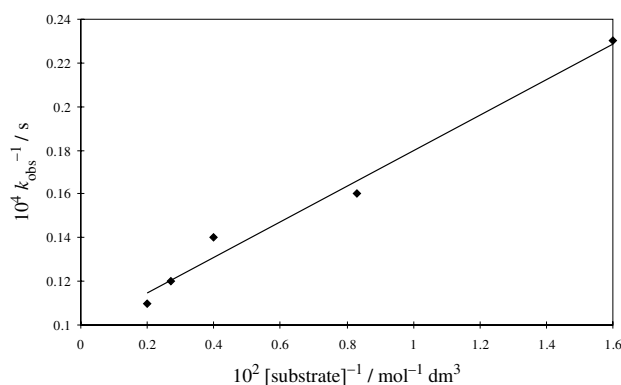
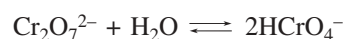


Figure 2: Michaelis-Menten plot for the oxidation of DL-methionine at 303 K.



The order of the reaction with respect to methionine was determined by varying its concentrations over a wide range (Table I). A plot of k_{obs}^{-1} versus $[\text{substrate}]^{-1}$ (Figure 2) ($r = 0.996$; $s = 0.012$) shows an intercept on the rate axis, indicating the Michaelis-Menten dependence on the concentration of the substrate. The catalytic activity of edta is shown in Table I. Edta enhances the conversion of methionine and the system can be characterised as:

$$k_{\text{obs}} = a + b [\text{edta}]$$

No levelling of rate constants took place at higher concentrations of (Figure 3) ($r = 0.995$; $s = 0.017$). There was no appreciable change in the rate with a change in ionic strength of the medium, affected by sodium perchlorate. No polymerisation is observed with acrylonitrile.

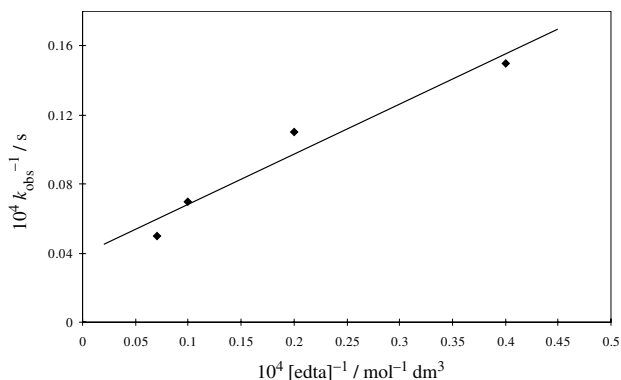


Figure 3: Michaelis-Menten plot for the oxidation of DL-methionine at 303 K.

The insensitivity of rates on added acrylonitrile rules out a free radical mechanism. Inhibition effect of Mn^{II} in this conversion is shown in Table II. Low values of relative permittivity (dielectric constant), ϵ_r of the medium favours the reactivity (Table III). A plot of $\log k_{\text{obs}}$ versus $1/\epsilon_r$ is slightly curved (Figure 4) ($r = 0.986$; $s = 0.034$) with a tendency to a positive slope. Heavy water (D_2O , 99.2 %) did not affect the reactivity of methionine. The lack of solvent isotope effect excludes the rate-controlling participation of water as a nucleophile.¹⁴ The solvent isotope effect on the

TABLE II. Effect of NaClO_4 , Mn^{II} and acrylonitrile (an) on the reaction rate at 303 K in 30 % aqueous acetic acid; [Oxidant] = 5.0×10^{-3} mol dm^{-3} , [Substrate] = 5.0×10^{-2} mol dm^{-3} , [edta] = 5.0×10^{-4} mol dm^{-3}

10^2 [NaClO_4] mol dm^{-3}	10^4 [Mn^{II}] mol dm^{-3}	10^3 [an] mol dm^{-3}	$10^4 k_{\text{obs}}$ s^{-1}
0.0	–	–	9.36
1.0	–	–	8.95
1.5	–	–	8.96
2.0	–	–	8.85
2.5	–	–	9.28
–	0.0	–	9.36
–	13.0	–	7.85
–	19.5	–	7.53
–	26.0	–	7.10
–	–	2.5	9.08
–	–	5.0	9.28
–	–	7.5	9.21
–	–	10.0	9.25

TABLE V. Rate constants for the oxidation of DL-methionine with Cr^{VI} in 30 % aqueous acetic acid; [Oxidant] = 5.0×10^{-3} mol dm^{-3} , [Substrate] = 5.0×10^{-2} mol dm^{-3} , [edta] = 5.0×10^{-4} mol dm^{-3}

Substrate	$10^4 k_{\text{obs}}$			ΔH^\ddagger kJ mol^{-1}	ΔS^\ddagger J K^{-1}	ΔG^\ddagger kJ mol^{-1}	r	s
	s^{-1}	s^{-1}	s^{-1}					
DL-methionine	9.36 ^(a)	12.52 ^(b)	15.79 ^(c)	18.24	243	91.87	0.998	0.015

(a) 303 K, (b) 313 K, (c) 323 K.

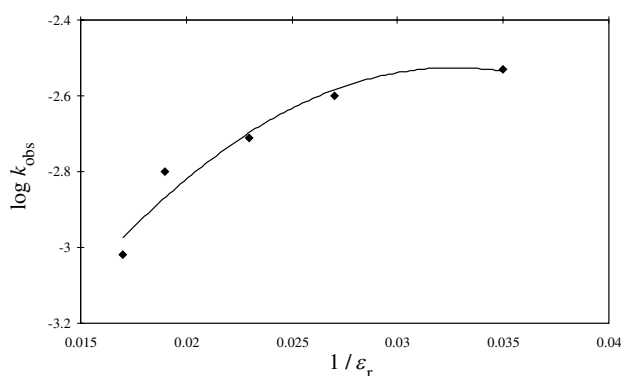


Figure 4: A plot of $\log k_{\text{obs}}$ vs. relative permittivity, ϵ_r^{-1} .

reaction rate is related to solvation effects in the two solvents.¹⁵ Activation parameters evaluated from Eyring's plot of $\ln k_{\text{obs}}/T$ versus $1/T$ ($r = 0.998$; $s = 0.015$), are listed in Table V.

Kinetic studies were carried out by adding 5.0×10^{-3} mol dm^{-3} of Co^{III} in the form of $\text{Co}(\text{NH}_3)_5\text{Cl}^{2+}$, a specific trapping agent for Cr^{II} . Co^{III} will oxidise Cr^{II} to Co^{II} .

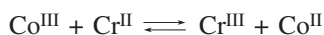
TABLE III. Effect of solvent composition on the reaction rate at 303 K; [Oxidant] = 5.0×10^{-3} mol dm^{-3} , [Substrate] = 5.0×10^{-2} mol dm^{-3} , [edta] = 5.0×10^{-4} mol dm^{-3}

$\varphi(\text{H}_2\text{O})$ %	$\varphi(\text{AcOH})$ %	$\epsilon_r^{(a)}$	$10^4 k_{\text{obs}}$ s^{-1}
70	30	58.0	9.36
60	40	50.6	15.75
50	50	43.2	21.02
40	60	35.8	25.03
30	70	28.4	29.80

(a) Relative permittivity values are calculated from the values of pure solvents.

TABLE IV. Effect of D_2O on the reaction of DL-methionine with Cr^{VI} at 303 K in 40 % aqueous acetic acid; [Oxidant] = 5.0×10^{-3} mol dm^{-3} , [Substrate] = 5.0×10^{-2} mol dm^{-3} , [edta] = 5.0×10^{-4} mol dm^{-3}

$\psi(\text{H}_2\text{O}, \text{AcOH}, \text{D}_2\text{O})$	$10^4 k_{\text{obs}} / \text{s}^{-1}$
60 : 40 : 0	15.75
58 : 40 : 2	15.86
54 : 40 : 6	15.66

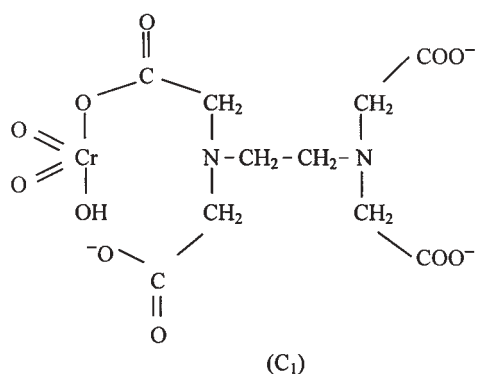


Absence of any effect on the rate rules out the involvement of Cr^{II} in the reaction sequence. Our results are generally in agreement with much of the literature on Cr^{VI} oxidations (*e.g.* Refs. 16–19), pointing to the assumption that Cr^{IV} is exclusively a one-electron oxidant. Interestingly, in some of the recent publications,^{20–22} clear evidence is given for the involvement of Cr^{II} as an intermediate.

Howard and Levitt²³ reported that the sequence of the reaction taking place in sulfides is $\text{R-S-R} \rightarrow \text{R-SO-R}$. Sulfide \rightarrow sulfoxide step is fast compared to the sulfoxide \rightarrow sulfone step. Methionine sulfoxide as the main product in the present study strongly supports this view. Further, the role of the other coordinating centres N and O as the sites of attack is unlikely.

The insignificant rate variations with ionic strength may be attributed to the absence of ion-ion interactions in the rate-determining step. The rate constants increase significantly with increasing the acetic acid content of the solvent, suggesting a facile reactivity in a medium of low dielectric constant. In general, such rate enhancements in a less polar solvent are ascribed to the facility of formation of Cr^{VI} ester.^{24–25} Quite likely, the formation of Cr^{VI} -edta or the $[\text{Cr}^{\text{VI}} \cdot \text{methionine} \cdot \text{edta}]$ as ternary intermediate in the present study is favoured in the medium of low permittivity.

The Cr^{VI} -edta mononuclear and binuclear complexes have been reported in literature.²⁶ The kinetic data in the present investigations can be rationalised by envisaging the formation of a Cr^{VI} -edta mononuclear complex (Scheme 1). The reaction proceeding through the binuclear complex pathway is minimal. The structure of the complex has been characterized.²⁶



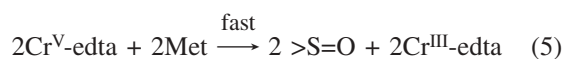
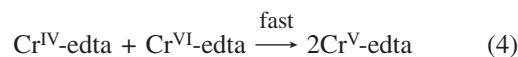
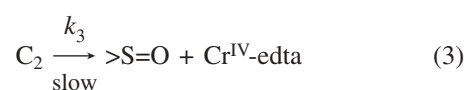
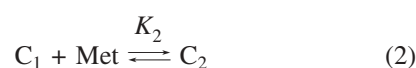
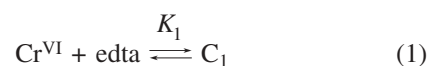
Scheme 1.

The purple coloured final product indicates the coordination of edta to Cr^{III} , the most stable chromium oxidation state.²⁶ It is reasonable to believe that the intermediate valence states Cr^{V} and Cr^{IV} would be in the form of Cr^{V} -edta and Cr^{IV} -edta.

Fairly linear plots between k_{obs}^{-1} versus $[\text{substrate}]^{-1}$ (Figure 2) and k_{obs}^{-1} versus $[\text{edta}]^{-1}$ (Figure 3) with definite intercepts indicate the formation of a ternary complex, $[\text{Cr}^{\text{VI}} \cdot \text{methionine} \cdot \text{edta}]$. Ternary intermediates of a similar type have been suggested in the edta catalysed Cr^{VI} oxidation of hydrazine,^{26–29} and edta catalysed chloramine-B oxidative chlorination of α -phenoxypropanoic acids.⁵ The proposal of a ternary intermediate has also been envisaged in the Cr^{VI} oxidation of I^- ,³⁰ isopropyl alcohol,³¹ *S*-phenylmercaptoacetic acid³² and cycloalkanones,³³ in the presence of oxalic acid.

Mechanism

Blank experiments ruled out the oxidation of edta under the experimental conditions maintained. Fractional order dependence on the concentrations of edta and methionine, facile reactivity in the low permittivity medium and the absence of free radicals during the course of the reaction could be described by the following scheme:



$$[\text{Cr}^{\text{VI}}]_{\text{t}} = [\text{Cr}^{\text{VI}}] + [\text{C}_1] + [\text{C}_2] \quad (6)$$

where $[\text{Cr}^{\text{VI}}]_{\text{t}}$ stands for the total Cr^{VI} concentration. Applying the equilibrium treatment, $[\text{Cr}^{\text{VI}}]$ can be determined:

$$\frac{-d[\text{Cr}^{\text{VI}}]}{dt} = k_3 [\text{C}_2] \quad (7)$$

$$= k_3 K_1 K_2 [\text{Met}] [\text{Cr}^{\text{VI}}] [\text{edta}] \quad (8)$$

$$\frac{-d[\text{Cr}^{\text{VI}}]}{dt} = \frac{k_3 K_1 K_2 [\text{Met}] [\text{Cr}^{\text{VI}}]_{\text{t}} [\text{edta}]}{1 + K_1 [\text{edta}] + K_1 K_2 [\text{Met}] [\text{edta}]} \quad (9)$$

$$k_{\text{obs}} = \frac{k_3 K_1 K_2 [\text{Met}] [\text{edta}]}{1 + K_1 [\text{edta}] + K_1 K_2 [\text{Met}] [\text{edta}]} \quad (10)$$

The rate law well characterises the reaction system. The absence of free radicals during the course of the re-

action, invariance of rate with Co^{III} and depressed reactivity in the presence of Mn^{II} account for step (4). Invariance of rate with Mn^{II} in the oxidation of L-methionine⁸ by aqueous solution of Cr^{VI} has been rationalised by disproportionation of Cr^{IV} .

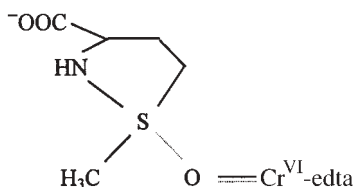


A similar observation was made by Haight and his coworkers³⁴ in the oxidation of hydrazine by Cr^{VI} . Assuming the reduction of Cr^{VI} to Cr^{IV} as the rate-limiting step is in agreement with most of the Cr^{VI} reactions reported in literature. Sulfur is more nucleophilic than nitrogen and it can supply electrons. The Cr^{VI} -edta complex can interact with methionine in a number of ways to give C_2 .

Electrophilic attack on Cr^{VI} -oxygen on the methionine can result in C_2 .

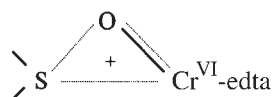


This type of transition state has been proposed for the oxidation of sulfides by pyridinium fluorochromate (pfc),³⁵ periodate ion,¹⁴ hydrogen peroxide,³⁶ pyridinium chlorochromate (pcc)³⁷ and 2,2'-bipyridinium chlorochromate.³⁸ A cyclic structure (Scheme 2) resembling the sulfurane intermediate proposed in the iodine oxidation of methionine³⁹ suffers high strain.



Scheme 2.

C_2 could be similar to the type of transition state suggested in the oxidation of sulfides by pcc⁴⁰ and pyridinium dichromate (pdc).¹¹



Scheme 3.

The cationic sulfur intermediate attack on water to give the sulfoxide is not supported by solvent isotope effect studies (Table IV). Highly negative ΔS^\ddagger value ($243 \text{ J K}^{-1} \text{ mol}^{-1}$) in the present investigation supports, to a certain extent, the structure presented in Scheme 3, since cyclic transition states always result in larger entropy of activation. Since the ΔS^\ddagger value is not exactly associated

TABLE VI. ΔH^\ddagger values for methionine oxidation^(a)

Oxidant	ΔH^\ddagger kJ mol ⁻¹	Reference
Cr(VI)edta	18.2	Present investigation
Quinolinium dichromate	44.0	41
Pyridinium chlorochromate	52.4	37
2,2'-Bipyridinium chlorochromate	57.9	38
Potassium dichromate	33.9	8

^(a) Evaluated from Eyring's plot of $\ln k/T$ vs. $1/T$.

with the slow rate-limiting step, no definite conclusions can be drawn. The kinetic data alone is insufficient to distinguish between all these possibilities. A rough comparison of ΔH^\ddagger values in the present study with those of uncatalysed Cr^{VI} oxidation of methionine indicates a facile oxidation process in the presence of edta, as shown in Table VI. It appears that the presence of edta decreases the enthalpic barrier to the reaction. The ternary complex offers the reaction a more favourable pathway and enhances the reactivity. Quite likely, the complexation with edta facilitates the internal electron transfer from substrate to oxidant, resulting in an enhanced reactivity.

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SAŽETAK

Kinetika i mehanizam oksidacije metionina kromom(VI): kataliza s pomoću edta

Subbiah Meenakshisundaram i Rajagopal Vinothini

Istraživana je kinetika oksidacije DL-metionina do sulfoksida s pomoću kroma(VI) u vodenoj otopini octene kiseline uz edta kao katalizator. Čini se da je aktivni elektrofil Cr^{VI}-edta. Niska dielektrična konstanta medija potpomaže reaktivnost. Ionska jakost i Mn^{II} ne utječu bitno na konverziju. Omjer $k(\text{D}_2\text{O}) / k(\text{H}_2\text{O}) \approx 1$ ukazuje na nepostojanje izotopnog efekta otapala. Visoke negativne vrijednosti ΔS^\ddagger ukazuje da je prijelazno stanje strukturirano. Povećana je reaktivnost objašnjena pretpostavljenim postojanjem ternarnog intermedijara.