Kinetics and Mechanism of the Oxidation of Some Tetracyclines by Chloramine-T

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The oxidation of oxytetracycline hydrochloride and tetracycline hydrochloride by chloramine-T (CAT) in aqueous acetic acid solution leads to the formation of the corresponding decarboxylated product. The reaction is first order with respect to the substrate as well as with respect to H^+ ion. The rate is independent of CAT concentration. Thermodynamic parameters have been calculated and mechanistic steps discussed.

INTRODUCTION

Sodium N-chloro-*p*-toluene sulphonamide (CH₃—⟨ O ⟩—SO₂·NClNa·3H₂O),

well-known as chloramine-T, is a potent oxidising agent as well as chlorinating agent in both acidic and alkaline media. It undergoes a two-electron change in its reactions and its redox potential is pH dependent. Literature survey[1-5] reveals that it has widely been used for oxidation and quantitative determination of a large number of inorganic and organic substances but only a few kinetic studies of the reactions have been made.

As a part of our programme on mechanistic studies of oxidation on drugs in general and tetracyclines[6-9] in particular we report here the kinetics of oxidation of tetracycline hydrochloride and oxytetracycline hydrochloride with chloramine-T (CAT).

EXPERIMENTAL

Chloramine-T (E. Merck, AR grade) was prepared by dissolving its exact amount in water. Its strength was determined iodometrically and stored in a dark-coloured flask. Aqueous solutions of oxytetracycline hydrochloride and tetracycline hydrochloride [obtained from Pfizer, India] were prepared by weighing their exact amount and dissolving in cold water. Their solutions were always prepared afresh before use.

Appropriate amount of sodium thiosulphate (AR, BDH) was dissolved in water and standardized by $CuSO_4$ solution using starch as indicator. A pinch of Na_2CO_3 was added to it to check any decomposition. Sodium perchlorate, glacial acetic acid, methanol, ammonium chloride and other chemicals were all of AR grade (BDH).

Stoichiometry

Different sets of reaction mixtures containing the substrate and the oxidant in the ratio 1 : 2, 1 : 3, 1 : 4 and 1 : 5 were allowed to stand for 12 h at 50°C under experimental conditions. Corresponding blank sets were also kept in the same bath for the same time period. After the reaction was complete, excess of the oxidant was titrated iodometrically.

$$w = \frac{(B - A) \times N \times M}{2 \times m}$$

where w = amount of the sample in mg

     B = Blank titration volume

     A = Titration volume with sample

     M = mol. wt. of the substrate

     N = normality of the hypo solution

 1 : 1 molar ratio was calculated.

RESULTS AND DISCUSSIOIN

In the oxidation of tetracyclines the rate of reaction was independent of CAT concentration, *i.e.*, zero order with respect to CAT, $K_c = \Delta x/\Delta t = $ slope.

The first order rate constants with respect to tetracycline and [H$^+$] ion were calculated by dividing the respective zero order rate constants in CAT by initial tetracycline (TC) and H$^+$ ion concentrations. It was found that k_0/[TC] and k_0/[H$^+$] values were fairly constant showing the order to be unity. Similar results were obtained for oxytetracycline hydrochloride also. Results are shown in Tables 1–3.

The rate law deduced is

$$\frac{- d[CAT]}{dt} = k \, [\text{substrate}] \, [H^+]$$

The hydrochlorides of tetracycline and oxytetracycline can be repre-sented as
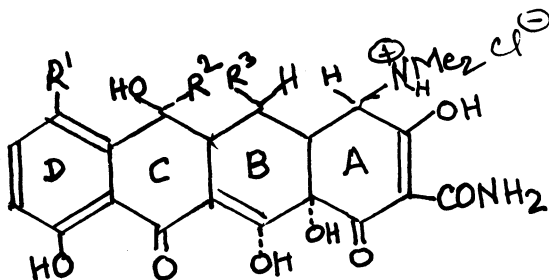
	R^1	R^2	R^3
Tetracycline hydrochloride	H	—CH$_3$	—H
Oxytetracycline hydrochloride	H	—CH$_3$	—OH

TABLE-1

$[CAT] \times 10^3 M$	$[TC] \times 10^2$	$[H^+] \times 10^3$ M at 35°C	$K_0 \times 10^7$	$[H^+] \times 10^3$	$[OTC] \times 10^2$	$K_0 \times 10^7$
0.8	1.0	2.5	8.42	5.00	1.00	5.10
1.0	1.0	2.5	8.65	5.00	,,	5.43
1.2	1.0	2.5	8.87	5.00	,,	5.48
1.4	1.0	2.5	8.77	5.00	,,	5.33
1.6	1.0	2.5	8.77	5.00	0.5	5.50
	0.5		4.28	5.00	1.0	2.74
	1.0		8.65	5.00	1.5	5.43
	1.5		12.90	5.00	2.0	8.04
	2.0		17.80	5.00	2.5	10.80
	2.5		21.50	5.00		13.90
		2.01	7.27	2.49		2.67
		2.49	8.65	5.04		5.43
		3.40	10.10	7.51		8.22
		4.02	14.90	10.01		10.40
		5.04	17.70	12.49		14.10

CAT—chloramine-T; TC—tetracycline; OTC—Oxytetracyline

TABLE-2

| Solvent composition methanol %	$[TC]$ $K_0 \times 10^7$	$[OTC]$ $K_0 \times 10^7$	$[NH_4Cl]$ $\times 10^2 M$	$[TC]$ $K_0 \times 10^7$	$[OTC]$ $K_0 \times 10^7$	$[NaClO_4]$ $\times 10^2 M$	$[TC]$ $K_0 \times 10^7$	$[OTC]$ $K_0 \times 10^7$
0	8.65	5.43	0.0	8.65	5.43	0.0	7.65	5.43
10	9.35	5.94	0.5	7.58	4.76	0.2	8.87	5.37
20	10.30	6.67	1.0	6.40	3.90	0.4	8.75	5.48
30	11.20	7.25	1.5	5.67	5.57	0.6	858	5.38
40	12.30	8.25	2.0	5.43	3.30	10.0	8.92	5.46
			decreases			independent		

Decrease in dielectric constant causes increase in reaction rate. Hence a negative dielectric effect

TABLE-3

Compound	Temp. (°C)	$K_0 \times 10^7$ $ML^{-1}sec^{-1}$	$K_0 \times 10^2$ $mol^{-1}sec^{-1}$	$A_0 \times 10^{-12}$ $mole^{-1}sec^{-1}$	ΔS^* eu	ΔH^* kcal $mole^{-1}$	ΔF^* kcal $mole^{-1}$
(TC)	30	5.01	2.01	4.27	−1.69	19.27	18.76
	35	8.65	3.47	4.37	−1.65	19.26	18.75
	40	14.20	5.70	4.27	−1.69	19.25	18.72
	45	24.50	9.84	4.47	−1.60	19.24	18.73
	50	38.70	15.54	4.27	−1.69	19.23	18.68
				4.33	−1.60	19.25	18.73
(OTC)	30	3.06	6.12	6.90	−0.73	20.27	20.49
	35	5.43	10.86	6.90	−0.73	20.25	20.47
	40	9.10	18.20	6.70	−0.76	20.25	20.49
	45	16.20	32.40	7.10	−0.68	20.24	20.46
	50	26.20	52.40	6.80	−0.77	20.23	20.48
				6.88	−0.73	20.25	20.48

These derivatives have three pK_a values[10] and analysis of the pK_a values indicates that their amphoteric forms were zwitterionic with both the charged sites on ring A. Similarly the diketoamide moiety is involved in usual keto-enol tautomerism. The dimensions of ring A indicate that the double bond is delocalised and the acidic hydrogen atom is attached to the oxygen atom of the amide group.
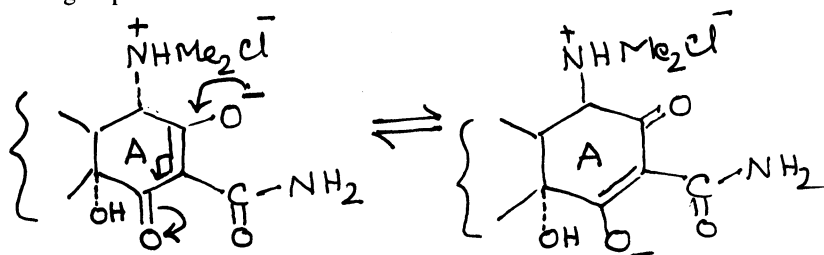
Other evidences for extensive electron delocalisation is provided by the high acidity of the enolic hydrogen atom. These observations show that —$CONH_2$ group is involved in keto-enol tautomerism and is protonated in acid media. This makes —$CONH_2$ group very labile and active site for the attack of any potent reagent. Many workers have reported that amides are hydrolysed in dilute acid and there is good correlation between log k and pH according to the Hamett-Zücker hypothesis.

It was observed that at very high [H^+] concentration the rate retarded and was found not to be linear to [H^+] concentration.

Thus the first step is hydrolysis of the amide group with hydronium ion to give β-keto acid through a slow and rate determining step. This undergoes oxidative decarboxylation to give the final product. It has been reported that the decarboxy-

lation is smooth if there is a strong electron attracting substituent at β or β′ position, which the substrate possesses.

Thus the role of proton is to bring about hydrolysis and CAT then brings about oxidative decarboxylation. Studies on the effect of NH_4Cl, change in polarity and various thermodynamic parameters for the activated species reveal that the hydrolysis of the β-keto amide group of tetracycline or oxytetracycline is slow and rate determining step, and not the oxidative decarboxylation.

Two probable mechanisms are suggested—one in which the β-keto acid itself undrgoes oxidative decarboxylation *via* intermediate complex formation with CAT, and the other in which the anion of the β-keto acid undergoes decarboxylation. Both the rates are shown below:

PATH I

β-keto acid   CAT

PATH II
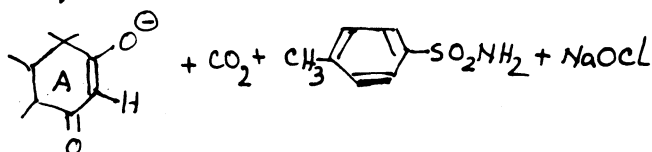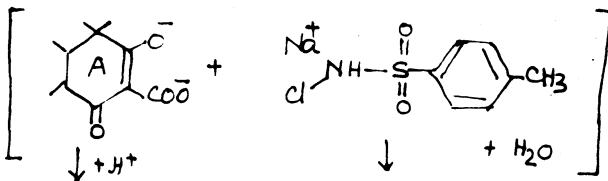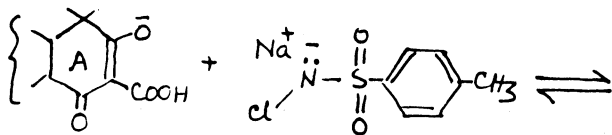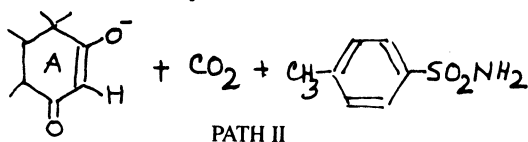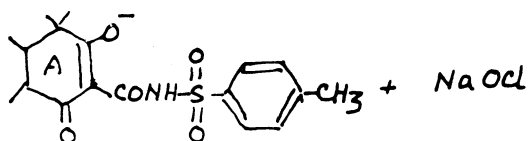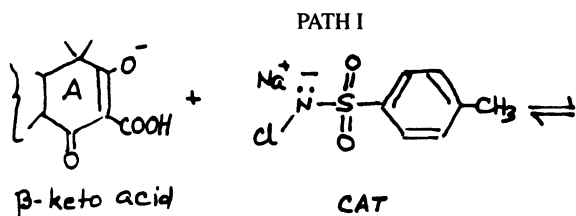
The rate law for the two courses suggests that probably both the mechanisms are operating simultaneously and they seem to be spontaneous and fast because the rate determining step is the hydrolysis of amide.

ACKNOWLEDGEMENTS

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