Oxidation Kinetics and Mechanistic Study of Some Aliphatic Aldehydes

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Abstract:- **Aliphatic aldehydes play a vital role in various chemical functions. A suitable mechanism consistent with the experimental results was proposed. Linearity of Exner's plot and constancy in $\Delta G^{\neq}$ values imply the operation of a similar type of mechanism in all amino acids. A rate law deciphering all the observed experimental facts was derived. The kinetics of oxidation of norfloxacin (NRF) by sodium N-chlorobenzene sulphonamide (Chloramine-B, CAB) has been studied in aqueous hydrochloric acid medium at 303 K. The reaction is first order with respect to [CAB] and [HCl], fractional order on [NRF]. Activation parameters were evaluated from the kinetic data at different temperatures. Negative entropy of activation indicated the involvement of a rigid complex in the activated state. The dielectric constant of the medium has a small effect on the rate. Ionic strength and the reaction product benzenesulphonamide have no effect on the reaction rate. The solvent isotope effect is studied. The reaction products are identified by spectral (IR and NMR) data. Rate equation is derived to account for the observed kinetic data and a probable mechanism has been proposed.**

Keywords**: kinetics, oxidation, norfloxacin, Chloramine-B.**

INTRODUCTION

Aliphatic aldehydes serve important functions in biological systems and play a significant role in metabolism. They are also employed in biochemical, microbiological and nutritional investigations. Some of them are employed as dietary supplements. Aliphatic aldehydes represent organism forerunners of essential biomolecules such as proteins, hormones, enzymes; also, they may serve as energy source, losing their amino group by two pathways: transamination and oxidative formination.[1]

The degradative metabolism of glutamic acid in animals involves oxidative deamination or transamination followed by oxidation of the resulting α-keto glutarate in the citric acid cycle.[2]

Chemically the majority of natural Aliphatic aldehydes are α-Aliphatic aldehydes, having the general formula $R(CH)NH_2COOH$. With the exception of glycine, the natural Aliphatic aldehydes contain one or more asymmetric carbon atoms and all of them are of laevo configuration with respect to L-glyceraldehyde.

Aliphatic aldehydes are widely distributed in the plant and animal kingdoms. Micro organisms synthesise the Aliphatic aldehydes from mineral and organic nitrogen sources. Their biosynthesis, however, requires one essential condition, viz., the structure and metabolism of an intact living cell.

Among the multiple functions that Aliphatic aldehydes fulfill in living cells is to serve as the monomer units from which the polypeptide chains of proteins are constructed. Most proteins contain, in varying proportions, the same twenty L-Aliphatic aldehydes. Many specific proteins contain, in addition, L-a-Aliphatic aldehydes derived from some of the basic twenty by processes that occur after formation of the polypeptide back bone. These 'unusual' Aliphatic aldehydes fulfill highly specific functions for the protein in question and thus increase biologic diversity. The kinds of Aliphatic aldehydes, the order in which they are joined together and their mutual spatial relationship dictate the three dimensional structures and biological properties of simple proteins. They are also major determinants of structure and function for the complex proteins that contain, in addition to Aliphatic aldehydes, haem, carbohydrate, lipid and nucleic acids.

The human diet must contain adequate quantities of ten essential L-α-Aliphatic aldehydes to support infant growth or to maintain health in adults since humans or any other higher animal cannot synthesize them. In the form of proteins, Aliphatic aldehydes perform a multitude of structural, hormonal and catalytic functions essential to life. It is thus not surprising that genetic defects in the metabolism of Aliphatic aldehydes can result in severe illness. Several comparatively rare genetic diseases of amino acid catabolism (e.g. phenylketonuria and maple syrup urine disease) will, if left untreated, result in

mental retardation and early death. Additional genetic diseases can result from an impaired ability to transport specific amino acid into cells. Since these transport defects typically result in the excretion of urine in increased amounts of one or more amino acid, they often are termed aciduria.

AIMS AND BACKGROUND

The chemistry of N-halo-N-sodium sulphonamides in aqueous solution has received considerable attention and the existing literature on the subject has been reviewed1 3.

These compounds in aqueous solution give several oxidising species and the concentration of each species depends on the pH and nature of the medium4,5. Chloramine-B, one such compound, has been used to understand the mechanism of oxidation of few medicinal compounds6–8.

Norfloxacin,(NRF)[1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline- 3-carboxylic acid] is a synthetic broad spectrum fluoroquinoline antibacterial agent for oral administration, which has *in vitro* activity against gram-positive and gram-negative aerobic bacteria. It inhibits deoxyribonucleic acid (DNA) synthesis and is bactericidal9,l0.

The kinetics and mechanism of oxidation of NRF in aqueous acetic acid containing HClO4 and also in NaOH has been studied11,12. These investigations revealed the considerable influence of the reaction medium on the oxidation kinetics. In order to have a comprehensive understanding of the oxidation mechanism of NRF under different experimental conditions, it was felt to investigate the influence of chloride ions on the kinetics of oxidation of NRF by Chloramines-B in acidic medium.

METHDOLOGY

Preparation of CAB and its purification have been reported in earlier communication13.

Aqueous solution of CAB was standardised iodometrically and preserved in brown bottle. NRF (Plama lab, India) was purified by CH2Cl2/MeOH (m.p. 227–228^{o}C) and used. All other chemicals were of analytical grade. Doubly distilled water was used to prepare the solutions. *Kinetics measurements*. The pseudo-first order condition was maintained by keeping [NRF]>>[CAB]. The reaction was carried out in glass-stoppered pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects. Requisite amounts of CAB, HCl and water (to keep the total volume constant for all the runs) were taken in the tube and thermostated at 303 K for thermal equilibrium.

A measured amount of NRF solution was also thermostated at the same temperature and rapidly added to a mixture in the boiling tube. The progress of the reaction was monitored up to two and a half-lives by iodometric determination of unreacted CAB in measured aliquot of the reaction mixture withdrawn at different time intervals.

The pseudo-first order rate constants (k') calculated were reproducible within ±3%. Regression analysis of the experimental data was carried out. *Stiochiometry and product analysis*. Reaction mixtures under conditions [CAB] >> [NRF] were equilibrated at 303 K in 1 $\times 10^{-1}$ mol dm^{-3} HCl solution for 24 h. The results showed the consumption of 4 mol of CAB per 1 mol of NRF. On the basis of analysis of the reaction products, the following stoichiometric equations are proposed:

$$C_{16}H_{18}N_3O_3F + 4RNClNa + 4H_2O \rightarrow C_{14}H_{18}N_3O_3F + 4RNH_2 + 4NaCl + 2CO_2 \quad (R = C_6H_5SO_2)$$

The reaction product of oxidant, benzenesulphonamide, was detected by TLC (Ref. 14). CO2 was identified by the lime-water test. The oxidation product of NRF (3-fluoro-4 piperazinyl-6-N-ethylaminophenylglyoxylic acid) was isolated and characterized by IR (Nicolet Impact 400D, FTIR) and NMR (Bruker, drx 500, FTNMR, SF =125.75 MHz) spectral studies.

IR (KBr) rmax cm–1: 1621s(C=O), 1729s(C=O)acid, 3059s(NH), 3400s(OH)
1H NMR(DMSO) ppm: 1.51 (ethyl protons), 8.03(1H,m), 7.58(1H,m), 4.79 (piperazinyl protons), 9.23 (OH,s), 8.28 (1H, NH, s).

The oxidation of NRF under different experimental conditions was investigated at various initial concentrations of the reactants in acidic medium.

Kinetics of oxidation of NRF (2.00×10^{-3} mol dm^{-3}) by the oxidant at constant concentration (1×10^{-1} mol dm^{-3}) of HCl was studied at various initial concentrations ([2–15] $\times 10^{-4}$ mol dm^{-3}) of CAB at 303 K. Plots of lg [CAB] versus time are linear indicating a first order dependence of the rate on [oxidant]. The constancy of rate constant ($k$obs) at different concentrations of oxidant evaluated from the integrated first order rate equation (Table 1) is a further evidence for the pseudo-first order dependence of the rate on [oxidant]. The order of the reaction with respect of [CAB] was found to be 1.00 ± 0.03. The oxidation was carried out with various

concentrations ([0.5 – 3.0] × 10^{-3} mol dm^{-3}) of NRF by using 2 × 10^{-4} mol dm^{-3} CAB in 1 × 10^{-1} mol dm^{-3} HCl. The rate of reaction increased with increasing [NRF] (Table 1). Plots of lg *k*obs versus [NRF]0 were linear with a slope of 0.60, indicating a fractional-order dependence on [NRF].

Table 1. Effect of varying oxidant, substrate and HCl concentrations on the reaction rate at 303 K

[CAB]x 10^4 (mol dm^{-3})	[NRF] x 103 (mol dm^{-3})	[HCL]x10 (mol dm^{-3})	K' x10^4 (S^{-1})
2.00	2.00	1.00	9.33
5.00	2.00	1.00	9.32
7.50	2.00	1.00	9.31
10.00	2.00	1.00	9.30
15.00	2.00	1.00	3.54
2.00	0.50	1.00	4.74
2.00	0.75	1.00	5.91
2.00	1.00	1.00	9.32
2.00	2.00	1.00	11.66
2.00	3.00	1.00	2.05
2.00	2.00	0.25	3.46
2.00	2.00	0.50	6.85
2.00	2.00	0.75	9.32
2.00	2.00	1.00	13.90
2.00	2.00	1.50	13.91

The reaction was carried out with 2 × 10^{-4} mol dm^{-3} oxidant and 2 × 10^{-3} mol dm^{-3} of NRF in the presence of various concentrations ([0.25 – 1.50] × 10^{-1} mol dm^{-3}) of HCl at 303 K. The rate increased with increase in [HCl] (Table 1). The reaction was first order with respect to [HCl]. At fixed [H^+], addition of NaCl did not affect the rate significantly. Hence the dependence of the rate on [HCl] reflected the effect of [H^+] only on the reaction. Therefore, the rate of reaction is directly proportional to [H^+] when the overall acid concentration was varied and the ratio k'/[H^+] is nearly a constant.

The reaction of CAB (2 × 10^{-4} mol dm^{-3}) and NRF (2 × 10^{-3} mol dm^{-3}) was carried out in the mixtures of methanol and water of various compositions (% v/v) containing HCl (1 × 10^{-1} mol dm^{-3}) at 303 K. The reaction rate increased with increase in MeOH content in the medium (Table 2).

Table 2. Effect of varying dielectric constant of medium on the reaction rate at 303 K
[CAB] = 2.0 × 10^{-4}mol dm^{-3}; [NRF] = 2.0 × 10^{-3} mol dm^{-3}; [HCl] = 0.10 mol dm^{-3}

%MeOH (v/v)	D	K' x10^4 (S^{-1})
0	76.72	12.06
5	74.54	15.10
10	72.36	16.30
20	67.46	19.60

The ionic strength of the medium was varied by adding sodium perchlorate (μ = 0.01 – 0.1 mol dm^{-3}), but this had negligible effect on the rate of the reaction. Hence, no attempt was made to keep it constant for kinetic runs. Addition of the reaction product, benzenesulfonamide (1 × 10^{-3} – 1 × 10^{-2} mol dm^{-3}) had no significant effect on the rate. The reaction rates were studied at different temperatures (283–323 K). From the linear Arrhenius plot of lg k' versus 1/*T*, values of composite activation parameters, energy of activation (*E*a), enthalpy of activation (Δ*H**), entropy of activation (Δ*S**), free energy of activation (Δ*G**) and lg *A* were computed. These results are compiled in Table 3.

Table 3. Temperature dependence on the reaction rate and activation parameters for the oxidation of NRF by CAB in acid medium
[CAB] = 2.0 × 10^{-4} mol dm^{-3}; [NRF] = 2.0 ×10^{-3} mol dm^{-3}; [HCl] = 0.1 mol dm^{-3}

Temperature (K)	K' x10^4 (S^{-1})		Activation parameters
283	3.00	E_a (kJ mol^{-1})	43.6
293	5.64	ΔH^* (kJ mol^{-1})	41.1
303	9.31	ΔG^*(kJ mol^{-1})	91.6
313	17.27	ΔS^*(JK^{-1} mol^{-1})	-166.6
323	30.61	Ig*A*	6.6

Addition of acrylamide solution to the reaction mixture in an inert atmosphere did not initiate polymerisation of the latter, indicating the absence of free radical formation in the reaction sequence.

DISCUSSION

Bishop and Jennings15, Morris et al.16 and Higuchi et al.17 have established the presence of several equilibria in acidified Chloramines-T (CAT) solutions. The work of Zilberg18, Mogilevski et al.19 and Mahadevappa et al.20 have indicated the

operation of similar equilibria in acidified CAB solutions. Chloramine-B ionises in aqueous solution, as follows:

$PhSO_2NCl \rightarrow PhSO_2NCl^- + Na^+$

The anion picks up a proton in acid solution to give monochloramine ($PhSO_2NH$ Cl), which can undergo disproportion and/or hydrolysis, to give the dichloramine, benzenesulphonamide and HOCl. Hence, the probable oxidising species are PhSO2NHCl, $PhSO_2NCl_2$ and HOCl. $PhSO_2NCl_2$ can be ruled out as the oxidising species in view of the strict first order dependence of rate on [CAB]. Similarly, a first order retardation of rate by benzenesulphonamide is expected, if HOCl is the reactive species. Since, these are not observed, the effective oxidising species in the rate-determining step could be conjugate acid ($PhSO_2NHCl$) in acid solution of CAB in the present system.

In the present investigations, oxidation of NRF by CAB in acid medium shows a fractional-order dependence on [NRF] and clearly indicated complex formation between the substrate and oxidant in an equilibrium step prior to the rate-limiting step.

However, the rate dependence on [H+] indicates the involvement of a neutral species in the rate-determining step (rds). The reaction product of CAB, benzenesulphonamide had no effect on the rate thus indicating that it was not involved in pre-equilibrium with oxidant.

Based on the above facts, the mechanism of oxidation of NRF by CAB in acid medium is best explained by scheme 1 to account all the observed kinetic data.

S c h e m e 1

$$\text{PhSO2NHCl} + \text{NRF} \overset{k}{\leftrightarrow} X \quad \text{fast (i)}$$

$$X + H^+ \xrightarrow{k} X' \quad \text{rate-limiting (ii)}$$

$$X' + 3\text{PhSO2NHCl} \rightarrow \text{products fast (iii)}$$

Assuming total concentration of CAB as [CAB]T = [RNHCl] + [X] with [H+]T >> [CAB]T , one could obtain:

$$[X] = \frac{K[CAB]T[NRF]}{1+K[NRF]} \quad (1)$$

Since,

$$\text{rate} = k[H+][X]$$

substituting the value of [X], one gets

$$rate = \frac{kK[CAB]T[NRF]}{1+K[NRF]} \quad (2)$$

Since, rate = $k$obs [CAB], after re-arrangement we get,

$$\frac{1}{kobs} = \frac{1+K[NRF]}{kK[NRF]}\frac{1}{[H+]} \quad (3)$$

Further, equation (3) can be re-arranged

$$\frac{\frac{1}{kobs}}{\frac{1+K[NRF]}{kK[H+][S]}\frac{1}{k[H+]}} = \quad (4)$$

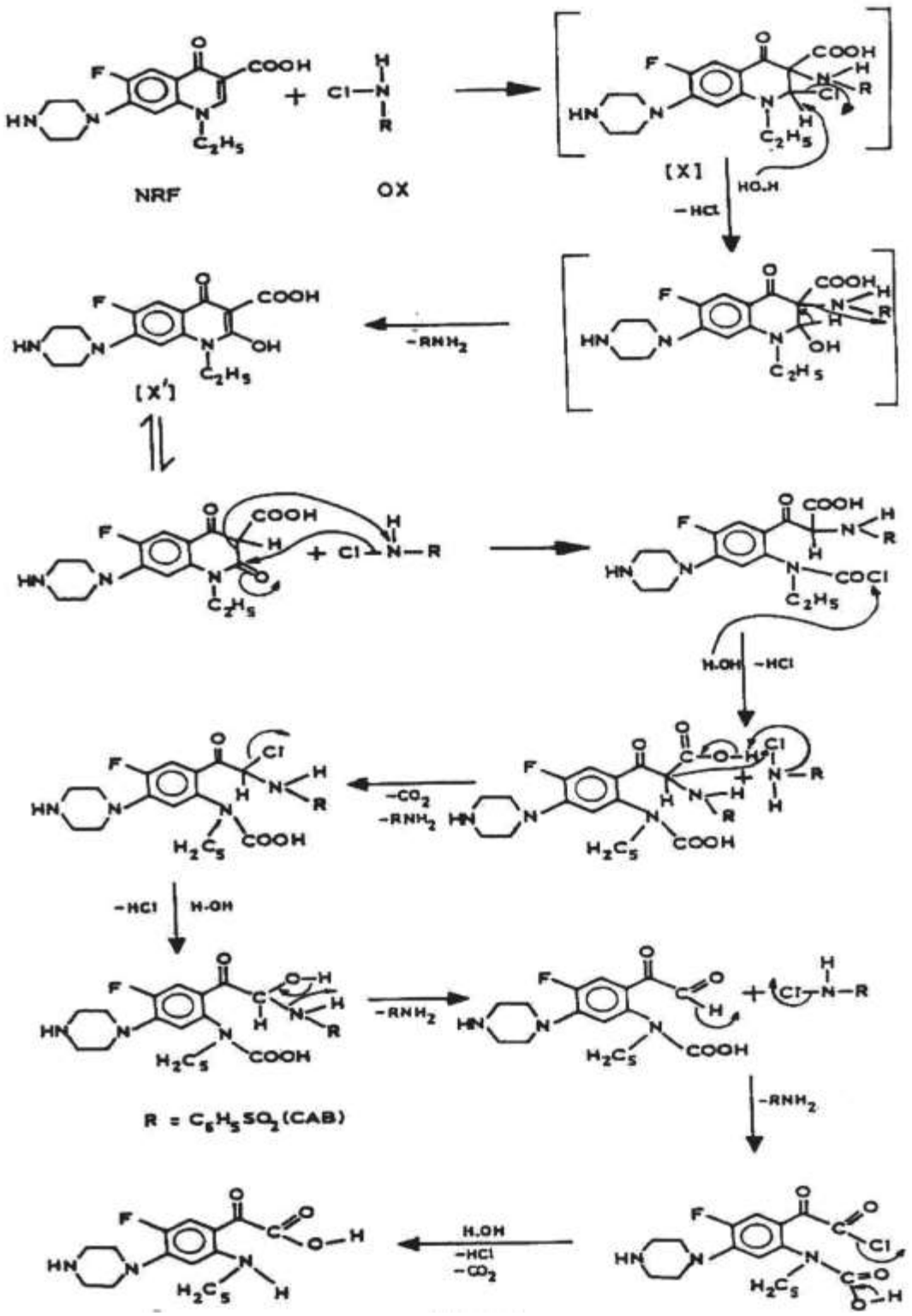
Based on equation (4), a double reciprocal plot of $k$obs versus [NRF] at constant HCl was found to be linear and the value of (kK) was calculated from the intercept.

From equation (3), plot of 1/$k$obs versus 1/[H^+] was found to be straight line passing through the origin. The value of (kK) was calculated from the slope of the plots and the 2 values were found to be same. The constancy of (kK) values indirectly supports the proposed mechanism for the oxidation of NRF.

The effect of varying solvent composition on the reaction kinetics has been described in detail in the well-known monographs21,22 . For the limiting case of zero angle of approach between 2 dipoles or an ion–dipole system, Amis 22 has shown that a plot of lg k' versus 1/D gives a straight line with a negative slope for a reaction between a negative ion and a dipole or between 2 dipoles, while a positive slope results for a positive ion and dipole interaction. The positive dielectric effect observed in the present studies clearly supports the positive ion and a dipole interaction reported.

Electron flow during the oxidation of NRF by CAB is depicted in reaction scheme 2. Electrophilic attack by the oxidant (RNHCl of CAB) on NRF results in the formation of X which on further hydrolysis, gives intermediate X′. Then X′ reacts stepwise with 3 mol of oxidant. A total of 4 mol of the oxidant is consumed to yield the final products. The proposed mechanism is in conformity with the observed kinetic data.

Scheme-2



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