Research Article

Oxidation of Norfloxacin by N-Chlorosuccinimide – A Kinetic Study

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ABSTRACT

The kinetics of oxidation of Norfloxacin (NRF) by N-Chlorosuccinimide (NCS) has been studied in aqueous hydrochloric acid medium at 303K. The reaction is first order with respect to [NCS], fractional order on [NRF]. Activation parameters were evaluated from the kinetic data at different temperatures. The dielectric constant of the medium has a small effect on the rate. Ionic strength and the reaction product, succinimide 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, Norfloxacin, N-Chlorosuccinimide, Oxidation.

INTRODUCTION

N-halogen compounds are known to be very good oxidizing agent.[1] N-Chlorosuccinimide (NCS) is a versatile reagent and its significance is not limited to Chlorination and Oxidation.[2] It is used as a source for chlorine in radical reactions and various electrophilic additions. It mediates and catalyses many chemical reactions including halocyclisation, formation of heterocyclic systems, formation of new carbon-carbon bonds, re-arrangements and functional group transformations. NCS can be used to prepare rubber additives and also used as an intermediate or a chlorinating agent in the synthesis of pharmaceuticals, especially tetracycline antibiotic. It is a source of positive halogen and the reagent has been exploited as oxidant for a variety of substrates. The kinetics of oxidation of alcohols, thiocyanate, thio semicarbazide, amines, sulphoxide, aromatic aldehydes[3-11] by NCS has been reported in literature.

Norfloxacin(NRF)[1-ethyl-6-fluro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid] is a synthetic broad –spectrum fluroquinoline antibacterial agent for oral administration , which has *in-vitro* activity against gram positive and gram negative aerobic bacteria, it inhibits deoxy ribonucleic acid(DNA) synthesis and is bactericidal.[12,13] The kinetics of oxidation of Norfloxacin by Chloramine- B and N-chlorobenzotriazole is already known.[14,15] However the kinetics of oxidation of Norfloxacin by NCS in aqueous HCl medium is not reported so far. Hence it is interest to know, the observed kinetic data, probable products and mechanism of oxidation of NRF by using NCS in acidic medium.

MATERIALS AND METHODS

Solutions were prepared by using double distilled water, commercial sample of NCS was used as such. Standard solution of NCS was prepared in water and its purity was checked iodometrically.[16-18] NRF (plama lab, India) was purified by CH_2Cl_2 /MeOH (m.p. 227°- 228°C) and used; all other chemicals were of analytical grade.

Kinetic measurements

The pseudo-first order condition was maintained by keeping [NRF]>>> [NCS]. The reaction was carried out in glass stoppered pyrex boiling tubes, whose outer surface was coated black to eliminate photochemical effects. Requisite amounts of NCS, HCl and water were taken in the tube and it was placed in an electrically operated thermostat maintained at 30^0 C for thermal equilibrium. A known volume of solution of NCS also equilibrated thermally at the same temperature and was rapidly added to the reaction mixture and the kinetics of the reaction was followed by estimating a known aliquot of the reaction mixture at different time intervals, iodometrically, using starch as indicator. The pseudo-first order at constants (k) calculated were reproducible within ±3%.

Stiochiometry

Excess of oxidant over NRF (C_{16} H_{18} N_3O_3F) was allowed to react in aqueous HCl medium. The residual oxidant was determined iodometrically after 24 hrs. The results showed the consumption of 4 moles of oxidant per mole of NRF. On the basis of analysis of the reaction products, the following stochiometric equations are proposed.

$C_{16}H_{18}N_3O_3F + 4RNCl + 4H_2O \rightarrow C_{14}H_{18}N_3O_3F + 4RNH + 4HCl + 2CO_2$

Where R= $(CH_2CO)_2NH$

Product analysis

The reduction product succinimide was detected by methods reported else were [19]; CO_2 was identified by the lime water test. After elimination of succinimide, the residual solution was introduced into column containing anion ion exchange resin in order to remove Cl^- ions. The final elute was concentrated to 30% and the amount obtained was stochiometric with the concentration of NRF used for the reaction. The oxidation product of NRF (3-fluoro-4-piperazinyl-6-N-ethylaminoglyoxylic 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) r_{max} cm^{-1}: 1621 s(C=O), 1729 s(C=O) acid, 3059 s(NH), 3400 s(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).

RESULTS AND DISCUSSION

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

Kinetics of oxidation of NRF [2×10^{-2} mol/dm^3] by the oxidant at constant concentration of HCl [1×10^{-1} mol/dm^3] was studied at various initial concentrations of NCS [2×10^{-3} mol/dm^3 - 10×10^{-3} mol/dm^3] at 303 K. plots of log [NCS] v/s time are linear with a slope 1.00 indicating a first order dependence of rate on [oxidant] (Table-I). The oxidation was carried out with various concentrations [2×10^{-3} mol/dm^3 - 3×10^{-2} mol/dm^3] of NRF by using [2×10^{-3} mol/dm^3] NCS in [1×10^{-1} mol/dm^3] HCl. The rate of reaction increased with increasing [NRF] (Table-I). Plots of log k_{obs} v/s [NRF], where linear with a slope 0.60, indicating a fractional dependence on [NRF].

The reaction was carried out with [2×10^{-2} mol/dm^3] NRF and [2×10^{-3} mol/dm^3] NCS in the presence of various concentrations [2.5×10^{-2} mol/dm^3 - 2×10^{-1} mol/dm^3] of HCl at 303 K. Plots of log k_{obs} v/s [HCl] were linear with slope of 0.83, indicating fractional order dependence on [HCl].

Effect of $[H^+]$ was investigated by varying [HCl] at constant $[Cl^-]$. Increase in $[H^+]$ ion increased the rate constant of the reaction. The plot of log k_{obs} v/s log $[H^+]$ is linear with slope 0.55 indicating fractional order dependence.

The effect of $[Cl^-]$ on the rate of reaction has also been studied by increasing the $[NaClO_4]$ at constant [HCl]. Addition of Cl^- at fixed $[H^+]$ increased the rate of the reaction. A plot of log k_{obs} v/s log $[NaClO_4]$ was linear with slope 0.30 indicating fractional order dependence of rate on $[Cl^-]$.

The reaction of NCS and NRF was carried out in the mixtures of methanol and water of various compositions containing HCl at 303K. The reaction rate slightly decreased with increase in MeOH content in the medium (Table-II).

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

10^2[NRF] (mol/dm^3)	10^3[NCS] (mol/dm^3)	10[HCl] (mol/dm^3)	10^5 k_{obs} (s^{-1})
2.00	2.00	1.00	5.80
2.00	2.50	1.00	1.45
2.00	5.00	1.00	1.28
2.00	7.50	1.00	4.35
2.00	10.00	1.00	6.06
0.20	2.00	1.00	4.14
0.30	2.00	1.00	1.79
1.00	2.00	1.00	2.96
2.00	2.00	1.00	5.92
3.00	2.00	1.00	4.84
2.00	2.00	0.25	5.37
2.00	2.00	0.50	4.18
2.00	2.00	1.00	5.72
2.00	2.00	1.50	4.03
2.00	2.00	2.00	4.09

Table 2: Effect of varying % of MeOH on the reaction rate at 303 K

% of MeOH	D	k x105(s-1)
5	74.55	2.303
10	72.37	2.210
15	70.19	2.200
20	67.48	2.193
25	65.3	2.184

Table 3: Effect of temperature on the rate of reaction and activation parameters

Temperature in K	$k^1 \times 10^5$ (s^{-1})	Activation parameters
303	5.603	Ea (KJ mol^{-1}) = 8.8366
313	6.0605	ΔH*(KJ mol^{-1}) = 6.2340
323	7.4847	ΔG*(KJ mol^{-1}) = 41.627
333	8.9089	ΔS*(jK-1 mol^{-1}) = -132.95
343	9.6282	log A = 2.315

Addition of one of the reaction product succinimide and change in ionic strength of the reaction medium had no significant effect on the rate of oxidation. The reaction rates were studied at different temperatures (303-343K). From the linear Arrhenius plot log k^1 v/s 1/T, values of composite activation parameters, energy of activation (Ea), entropy of activation (ΔS*), enthalpy of activation (ΔH*), free energy of activation (ΔG*) and log A are computed (Table-III).

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

The active oxidizing species has to be identified, before suggesting a most probable mechanism. The nature of the active oxidizing species and the mechanism depend on the nature of the halogen atom, the groups attached to the nitrogen and the reaction condition. Under the experimental conditions studied, HOCl, N^+HCS, Cl_2 and NCS itself in aqueous solution can be the possible oxidizing species. Cl_2 can be ruled out as the oxidizing species in view of the strict first order dependence of rate on [NCS]. Similarly, a first order retardation of rate by succinimide is expected, if HOCl is the reactive species. Since these are not observed, the effective oxidizing species in the rate determining step could be conjugate acid (N^+HCS) in acid solution of NCS in the present system. The oxidation of NRF by NCS in acid medium shows a fractional order dependence on [NRF] and clearly indicated complex formation b/w 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. The reaction product of NCS, succinimide 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 NCS in acid medium is best explained by scheme 1 to account all the observed kinetic data.

The protonated NCS reacts with the substrate scheme 2 to form the intermediate X. The intermediate X undergoes hydrolysis to give X^I. Further, X^I decomposes to give CO_2, HCl, RNH_2 and oxidation product.

$$NCS + H^+ \underset{}{\overset{k_1}{\rightleftharpoons}} N^+HCS$$

$$N^+HCS + [S] \xrightarrow{k_2} X$$

$$X + H_2O \longrightarrow Products$$

Scheme 1

Therefore,

Rate = $k_2 [N^+HCS] [S]$

The total effective concentration of oxidizing agent is

$[NCS]_t = [NCS] + [N^+HCS]$

$$k_1 = \frac{[N^+HCS]}{[NCS]\ [H^+]}$$

Therefore,

$$[NCS] = \frac{[N^+HCS]}{k_1[H^+]}$$

$$[N^+HCS] = \frac{k_1 [H^+]\ [NCS]_t}{1 + k_1[H^+]}$$

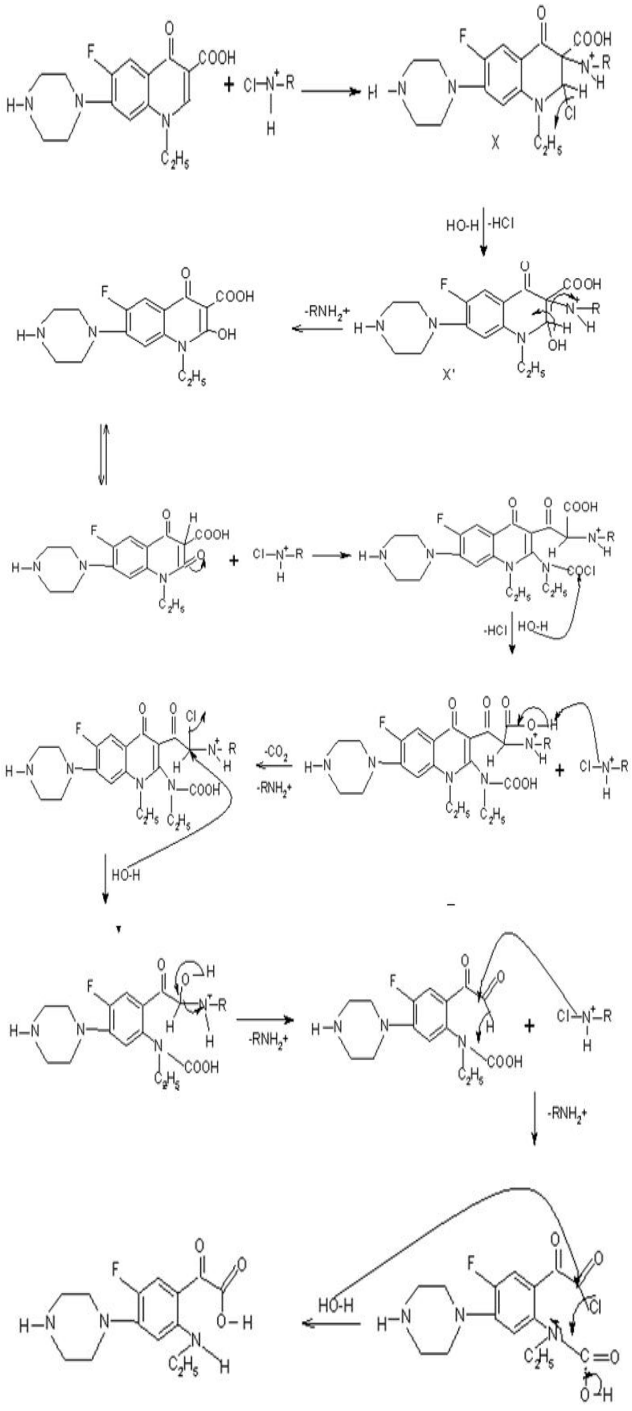
Therefore

$$Rate = \frac{k_2\, k_1 [H^+]\ [NCS]_t [S]}{1 + k_1[H^+]}$$

Since, rate= $k^1 [NCS]_t$ after rearrangement we get

$$\frac{1}{k^1} = \frac{k_1[H^+] + 1}{k_2\, k_1 [H^+]\ [S]}$$

$$\frac{1}{k^1} = \frac{1}{k_2\, k_1 [H^+]\ [S]} + \frac{1}{k_2 [S]}$$



Scheme 2

CONCLUSION

Oxidative cleavage of Norfloxacin with NCS in hydrochloric acid medium has been studied. The active species of NCS was found to be $N^{+}HCS$. The stoichiometry of the reaction was found to be 1:4 and the oxidation products were identified by spectral studies. An overall mechanism sequence is proposed and the rate law is derived.

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