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N-Chloropyrazinamide Oxidation of Chalcones: Kinetics And Mechanistic Studies

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Abstract: Kinetic studies on the oxidation of chalcones by N-chloropyrazinamide (NCPZA) investigated in aqueous acetic acid medium shows a zero order dependence on [NCPZA], [H^+] and [Cl^-]. Variation in ionic strength and pyrazinamide has also been studied. Decrease in dielectric constant of the medium, increases the rate. The reactions are studied at different temperatures and thermodynamic activation parameters have also been computed. The probable mechanism and rate law for the observed kinetics have been suggested.

Keywords: kinetics, oxidation, mechanism, chalcones, N-chloropyrazinamide.

INTRODUCTION

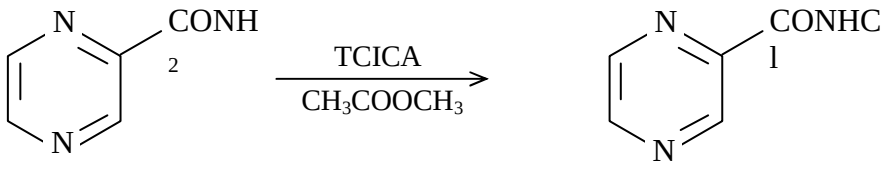
N-halo compounds are being used in kinetics, analytical[1], organic structural investigations and in synthesizing organic substrates[2]. The versatile nature of these compounds is due to their ability to act as sources of halonium ions, hypohalite species and nitrogen anions which act as both bases and nucleophiles. N-halo compounds are referred to as positive halogen compounds. N-chloropyrazinamide[3] (NCPZA) is a new, mild, stable and efficient oxidant. Pyrazinamide (PZA) is a drug used to treat tuberculosis. The drug is largely bacteriostatic, but can be bacteriocidal on actively replicating tuberculosis bacteria. Pyrazinamide in conjuction with rifampin is a preferred treatment for latent tuberculosis. It is a potent antiuricosuric drug and consequently has an off-label use in the diagnosis of causes of hyperuricemia and hyperuricosuria.

Chalcones undergo a variety of chemical reactions and are found useful in the synthesis of variety of heterocyclic compounds. Chalcones have been used as intermediate for the preparations of compounds having therapeutic value. Literature review reveals that chalcone derivatives exhibit diverse pharmacological activities[4-12] such as potential cytotoxic agents, antimicrobial agents, antiviral, anti-inflammatory, anesthetics, mydriatics etc. Hence the study becomes important from the biological point of view.

An extensive literature survey reveals that the kinetics and mechanism of oxidation of chalcones have been carried out using various oxidants like trichloroisocyanuric acid[13], pyridinium chlorochromate[14], acid bromate[15], N-chloronicotinamide[16], hexacyanoferrate (III)[17], N-chlorosuccinimide[18], chloramine-T[19], morpholinium chlorochromate[20], peroxydisulphate[21] and periodate[22]. The results of kinetics of oxidation of chalcones *viz*., benzylidene acetophenone (BAP), *p*-chlorochalcone (PCC), *m*-chlorochalcone (MCC), *p*-nitrochalcone (PNC), *m*-nitrochalcone (MNC), *p*-methoxychalcone (PMeOC) and *p*-methylchalcone (PMC) with NCPZA in aqueous acetic acid medium has been reported with a view to probe the mechanism of oxidation.

EXPERIMENTAL

Chalcones were prepared by condensing aryl ketones with aromatic aldehydes in presence of suitable condensing agents[22]. The derivative N-chloropyrazinamide, the oxidant in the present study was prepared by the chlorination of pyrazinamide using trichloroisocyanuric acid (TCICA) (Fig. 1). Standard solution of NCPZA was prepared fresh in water and its purity was checked iodometrically.



Pyrazinamide (PZA) N-chloropyrazinamide (NCPZA)

Fig. 1 Reaction for the synthesis of N-chloropyrazinamide

Acetic acid (AnalaR, indifferent from chromic acid) was used as such. Perchloric acid (AnalaR) was used as a source of $[H^+]$. Sodium chloride (Merck) was used as a source of $[Cl^-]$. Conducitivity water was used throughout the study.

KINETIC MEASUREMENTS

The reaction was carried out under pseudo-first order condition ([chalcone] >> [NCPZA]). The reaction was followed potentiometrically by setting up a cell made up of the reaction mixture into which a smooth platinum wire and a reference electrode (SCE) were dipped. The emf of the cell was measured periodically using a digital potentiometer (Equip-tronics dual channel potentiometer EQ-603). The pseudo-first order rate constants computed from the plots of log $(E_t - E_\infty)$ against time were reproducible within ± 3%.

Stoichiometry and product analysis

The stoichiometry of the reaction was determined by taking excess of [NCPZA] over [benzylidene acetophenone]. A mixture of NCPZA (0.04 M), benzylidene acetophenone (0.02 M), perchloric acid (0.2 M) and sodium chloride (0.2 M) was made up to 25 ml with 80% acetic acid - 20% water mixture (v/v). The contents of the reaction flask were kept for 24 h. After the completion of the reaction, the excess oxidant was determined iodometrically. The stoichiometry was found to be 1:1. Similar stoichiometric experiments were carried out for all the substituted chalcones. In all the cases, the stoichiometry was found to be 1:1.

$$RCH = CHCOC_6H_5 + C_4H_3N_2CONHCl + 2\ H_2O \longrightarrow RCOOH + C_6H_5CH_2CHO + C_4H_3N_2CONH_2 + HCl$$

where R = C_6H_5, *p*-Cl C_6H_4, *m*-Cl C_6H_4, *p*-NO_2 C_6H_4, *m*-NO_2 C_6H_4, *p*-OCH_3 C_6H_4, *p*-CH_3 C_6H_4

A mixture of chalcone (0.03 M), NCPZA (0.02 M), $HClO_4$ (0.20 M) and NaCl (0.20 M) was prepared in 80% aqueous acetic acid mixture. The mixture was allowed to stand for 24 h to ensure the completion of the reaction. The residual mixture was then extracted with ether. The ether layer was separated and dried. The product was found to be the corresponding substituted benzoic acid and phenyl acetaldehyde.

RESULTS AND DISCUSSION

Under the condition ([chalcone] >> [NCPZA]), the plots of log ($E_t - E_\infty$) (where E_t is the emf of the cell at time t and E_∞ the corresponding value at the completion of the reaction) versus time are linear indicating first order dependence of rate on [NCPZA]. The pseudo-first order rate constant does not change with increase in concentration of the oxidant. Increase in [chalcone] has no significant effect on the rate of oxidation which is evident from the constancy in rate values.

The effect of $[H^+]$ is investigated by varying $[HClO_4]$ at constant [NaCl] (Table 1). The rate increases with increase in $[HClO_4]$. The plots of log k_{obs} versus log $[H^+]$ are linear with positive unit slope indicating first order dependence on $HClO_4$. The effect of $[Cl^-]$ is studied by varying $[HClO_4]$ at constant $[H^+]$ (Table 1). Increase in [NaCl] has positive effect on the rate. The plots of log k_{obs} versus log $[Cl^-]$ are linear with unit slope indicating first order dependence of rate on [NaCl].

To confirm the order with respect to $[H^+]$ and $[Cl^-]$, the reaction has been investigated at several initial concentration of HCl (Table 1). The rate increases with increase in [HCl] and the plots of log k_{obs} versus log [HCl] are linear with slope around 2.0. This confirms that the order with respect to each $[H^+]$ and $[Cl^-]$ is found to be one.

An increase in the rate constant is noticed on decreasing the dielectric constant of the medium (Table 1), indicating the formation of less polar activated complex than the reactant molecule[23, 24].

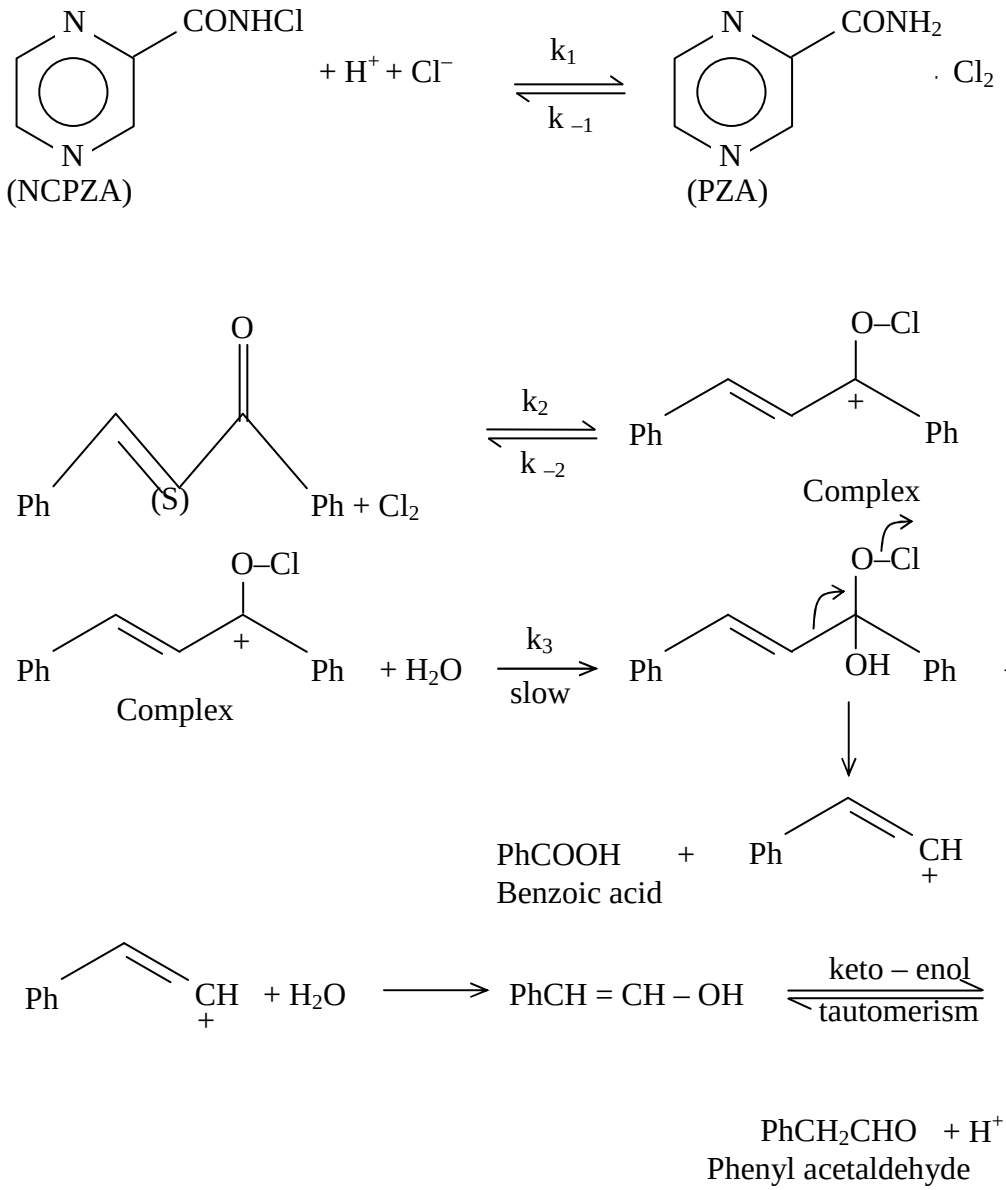
Addition of pyrazinamide (PZA) has been studied at different initial concentration of pyrazinamide. It is found that the rate has no significant effect with increase in [PZA]. Addition of $NaClO_4.H_2O$ to the reaction mixture has negligible effect on the rate. The reaction mixture fails to initiate polymerization of aqueous acrylamide solution, showing the absence of free radicals.

The oxidation of all the substituted chalcones are studied at different temperatures (313-333 K), keeping other experimental conditions constant. The Arrhenius plots of log k_{obs} versus 1/T are linear. The Arrhenius and thermodynamic activation parameters are evaluated (Table 2).

MECHANISM

Before suggesting a most probable mechanism, the active oxidizing species has to be identified. Under the experimental conditions, the possible oxidizing species[25] are Cl_2, HOCl, H_2OCl, $NCPZAH^+$ and NCPZA itself in aqueous solution. The oxidation of alcohols and aliphatic ketones by N-chlorosuccinimide[26] (NCS) and N-bromosuccinimide[27] (NBS) have been reported to take place through the intermediate forms of protonated species of the oxidant like $NCSH^+$ and $NBSH^+$.

If $NCPZAH^+$ is the active oxidant, the reaction must show hydrogen ion catalysis only. Since both hydrogen and chloride ions are found to catalyze the reaction in the present case, molecular chlorine has been assumed to act as the effective oxidant. It has been reported that in aqueous acidic solutions in presence of chloride ion, the oxidant produces a steady, but small, concentration of molecular chlorine[28].



where NCPZA = N-chloropyrazinamide, PZA = pyrazinamide, S = Chalcone

Derivation of rate law

rate = k_3 [Complex]

Applying steady state approximation to the molecular chlorine and the complex, the following rate law is deduced.

$$k_1 [NCPZA] [H^+] [Cl] - k_{-1} [PZA] [Cl_2] - k_2 [Cl_2] [S] = 0$$

$$[Cl_2] = \frac{k_1 [NCPZA] [H^+] [Cl^-]}{k_{-1} [PZA] + k_2 [S]}$$

$$k_2 [Cl_2] [S] - k_{-2} [Complex] - k_3 [Complex] = 0$$

$$[Complex] = \frac{k_2 [Cl_2] [S]}{k_{-2} + k_3}$$

Substituting $[Cl_2]$ value in the above equation, we get

$$[Complex] = \frac{k_2 \{k_1 [NCPZA] [H^+] [Cl^-]\} [S]}{k_{-2} + k_3\{k_{-1} [PZA] + k_2 [S]\}}$$

Assuming $k_{-1} [PZA] << k_2 [S]$,

$$rate = \frac{k_1 k_3 [NCPZA] [H^+] [Cl^-]}{k_{-2} + k_3}$$

The above rate law accounts for the first order dependence of rate on [NCPZA], $[H^+]$, $[Cl^-]$ and zero order dependence on [chalcone].

The mechanism is further supported by the value of energy of activation and other thermodynamic activation parameters. The high positive values of free energy of activation ($\Delta G^{\#}$) and enthalpy of activation ($\Delta H^{\#}$) indicates that the transition state is highly solvated, while the value of negative entropy of activation ($\Delta S^{\#}$) suggests that the activated complex is cyclic nature[29].

Table 1: Effect of variation of [BAP], [NCPZA], [HOAc], [$HClO_4$], [NaCl], [HCl] and [PZA] on the rate of oxidation at 323 K

[BAP] 10^2 (M)	**[NCPZA] 10^3 (M)**	**HOAc-H_2O % (v/v)**	**[$HClO_4$] (M)**	**[NaCl] (M)**	**[HCl] (M)**	**k_{obs} 10^3 (s^{-1})**
0.5	3.0	80-20	0.20	0.20	-	2.28
1.0	3.0	80-20	0.20	0.20	-	2.29
1.5	3.0	80-20	0.20	0.20	-	2.47
2.0	3.0	80-20	0.20	0.20	-	2.37
2.5	3.0	80-20	0.20	0.20	-	2.39
1.0	**1.0**	80-20	0.20	0.20	-	2.29
1.0	**2.0**	80-20	0.20	0.20	-	2.21
1.0	**3.0**	80-20	0.20	0.20	-	2.29
1.0	**4.0**	80-20	0.20	0.20	-	2.23
1.0	**5.0**	80-20	0.20	0.20	-	2.26

1.0	3.0	**65-35**	0.20	0.20	-	0.52
1.0	3.0	**70-30**	0.20	0.20	-	0.75
1.0	3.0	**75-25**	0.20	0.20	-	1.27
1.0	3.0	**80-20**	0.20	0.20	-	2.29
1.0	3.0	**85-15**	0.20	0.20	-	4.25
1.0	3.0	80-20	**0.10**	0.20	-	1.07
1.0	3.0	80-20	**0.15**	0.20	-	1.56
1.0	3.0	80-20	**0.20**	0.20	-	2.29
1.0	3.0	80-20	**0.25**	0.20	-	2.72
1.0	3.0	80-20	**0.30**	0.20	-	3.24
1.0	3.0	80-20	0.20	**0.10**	-	1.13
1.0	3.0	80-20	0.20	**0.15**	-	1.63
1.0	3.0	80-20	0.20	**0.20**	-	2.29
1.0	3.0	80-20	0.20	**0.25**	-	2.89
1.0	3.0	80-20	0.20	**0.30**	-	3.29
1.0	3.0	80-20	-	-	**0.10**	0.58
1.0	3.0	80-20	-	-	**0.15**	1.44
1.0	3.0	80-20	-	-	**0.20**	2.29
1.0	3.0	80-20	-	-	**0.25**	4.01
1.0	3.0	80-20	-	-	**0.30**	5.26

Table 2: Effect of temperature on the reaction rate

[Chalcone] = 1.0×10^{-2} M [NCPZA] = 3.0×10^{-3} M
[$HClO_4$] = 2.0×10^{-1} M [NaCl] = 2.0×10^{-1} M
Solvent (v/v) = 80% CH_3COOH - 20% H_2O

Temp (K)	**$k_{obs} \times 10^3$ (s^{-1})**						
	BAP	**PCC**	**MCC**	**PNC**	**MNC**	**POMeC**	**PMC**
313	0.90	0.77	0.89	0.93	0.88	0.84	0.80
318	1.61	1.50	1.58	1.39	1.46	1.22	1.34
323	2.29	2.16	2.23	2.34	2.52	2.12	2.26
328	3.85	3.30	3.99	3.93	3.67	3.63	3.54
333	5.33	5.30	5.33	5.02	5.24	4.91	5.05

Table 3: Thermodynamic activation parameters for the oxidation of chalcones

[Chalcone] = 1.0×10^{-2} M [NCPZA] = 3.0×10^{-3} M
[$HClO_4$] = 2.0×10^{-1} M [NaCl] = 2.0×10^{-1} M
Solvent (v/v) = 80% CH_3COOH - 20% H_2O

Chalcone	**E_a (kJ mol^{-1})**	**$\Delta H^{\neq}$ (kJ mol^{-1})**	**$\Delta G^{\neq}$ (kJ mol^{-1})**	**$\Delta S^{\neq}$ (JK^{-1} mol^{-1})**	**log A**
BAP	77.1	74.4	83.6	- 28.4	13.8
PCC	80.6	77.9	85.6	- 24.0	14.3
MCC	78.1	75.5	84.2	- 27.1	14.0
PNC	76.5	73.8	83.2	- 29.2	15.3
MNC	77.9	75.2	84.1	- 27.4	13.9
POMeC	80.1	77.4	85.4	- 24.7	16.9
PMC	80.8	78.1	85.7	- 23.6	15.3

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