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Oxidation of few Substituted Phenols and Reaction Mechanism by Heterocyclic Pyrazinium Chlorochromate and It's Biological Activity

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ABSTRACT

The current investigation focuses on the oxidation of phenol (Phenylic acid) and a few mono substituted phenols in a liquified ethanoic acid medium with pyrazinium chorochromate (PzCC) support. The reaction showed a first kinetic model in PzCC but a fractional order in phenols. The low dielectric constant of the process, which is helped by hydrogen ions, promotes the reaction. The reaction's speed is unaffected by an increase in ionic strength. *Meta*-substituted phenols, which rely on the field effect for oxidation, are more susceptible to the delocalized effect than *para*-substituted phenols. The positive proportionality constant (ρ) indicates the presence of an electron deficit reaction site in the slow stage. Non-linearity in the Hammett plot was seen for all of the substituted phenols. An efficient mechanism and rate law were proposed following the computation of the activation and thermodynamic variables. Several *Gram-positive* and *Gram-negative*, including *Entrococcus*, *Proteus vulgaris, Mycobacterium tuberculosis*, and fungi, Including *A. niger*, Fusarium, and *Trichoderma*, were examined for the antibacterial activity of the compound PzCC using the agar well diffusion method.

Keywords: Pyrazinium chlorochromate, Proportionality constant, Hammett plot, Rate law, Phenols, Antibacterial activity.

INTRODUCTION

Herbicides, medications, and nylon are all produced using phenylic acid (also known as phenol) and its derivatives. Phenylic acid is proven to damage the environment and kill out living things at low concentrations, according to studies[1,2]. There are numerous conventional method adopted to minimize the pathogenic nature of phenylic acid (C_6H_5OH) in water resources available in India, and the permissible limit in drinking water is 1ppb (0.001ppm). To oxidise various functional groups in synthetic organic chemistry, a variety of oxidants have arisen[3-5]. Due to the two-nitrogen atoms present, the pyrazine moiety has been found to have biological activity.

When the Cr(VI) is employed as an oxidizing agent it is aggressive and possess serious threat to all living creatures. The highly reactive nature is reduced by linking it with a heterocyclic nuclei and therefore its toxic nature is also minimized. By this way the pyrazinium chlorochromate is prepared and the aggressive nature is passified. They have been proven to be incredibly mild, selective, regiospecific, and regioselective[9,10], and they help in the oxidation of Cr^{+6} to Cr^{+3}, which is non-toxic to the environment[7,8] and many scientists working in organic chemistry[11,12] employ pyrazinium chlorochromate (PzCC), one of its kind. The oxidation of phenol and substituted phenols has drawn the attention of numerous researchers[13,14]. The literature review revealed that there are no known reports of pyrazinium chlorochromate in acetic acid oxidising phenols. The reactivity, correlation, and oxidation of a few meta and para substituted phenols were attempted to be studied utilising chromium(VI) oxidant in aqueous acetic acid medium.

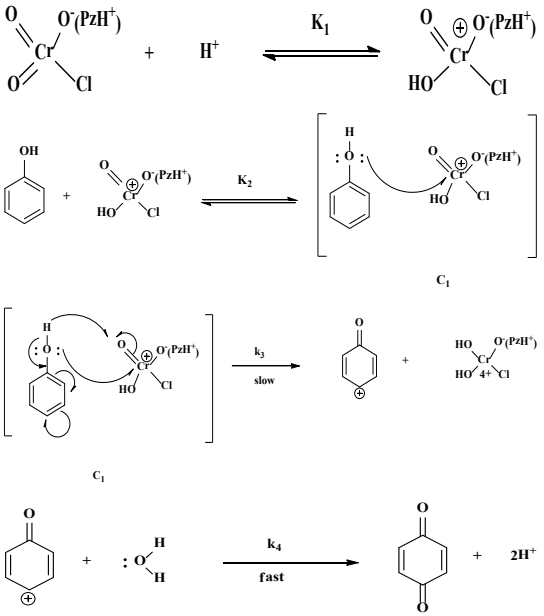
MATERIALS AND METHODS

The standard procedure was used to prepare the pyrazinium chlorochromate[15], while the remaining chemicals were AnalaR grade, the phenols with meta and para replacements were obtained and distilled prior to use. The absorption of the phenylic acid was greater compared to pyrazinium chlorochromate (PzCC), so pseudo first order conditions were applied. The reaction was experimented at a fixed temperature of about 0.1K and the variation in the concentration of the oxidant [PzCC] was studied using colorimeter (470nm). The products or reactants weren't absorbed by this wavelength. Linear relationship with r=0.991 was observed for 85% completion of the reaction from the log absorbance of the reactant with time. Less than 3% of the kinetic runs could be repeated. From the study for the oxidant (pyrazinium chlorochromate) first order kinetics was recorded and for all the substituted phenols, fractional order kinetics was seen. During the kinetic measurements for all the runs, one mole of pyrazinium chlorochromate consumed two moles of phenylic acid. Infrared, ultraviolet, and mass spectroscopy were used to verify the produced quinone after the solvent had been evaporated.

RESULTS AND DISCUSSION

For the substituted phenols, rates and kinetic data were obtained. The oxidant's reaction was first-order, and the plot's linearity and high correlation coefficient (r=0.991) were also favorable. With a slope value of 0.667, the log k_1 against log [S] plot showed that the reaction rate increased as the substrate concentration increased. The addition of sodium perchlorate ($NaClO_4$), which must affect the medium's ionic strength but has no impact on the reaction's pace, confirms the existence of ionic species in the slow phase. The reaction speed increased with the increase in the perchloric acid concentration [H^+]. The presence of a protonated oxidant in the reaction was established with the regression value of 0.993 on log k_1 vs log [acid] plot. The relationship between log k_1 and 1/D was plotted (r=0.999, B=+11.92) and showed that the rate increased as the percentage of acetic acid rose. The interface concerning the neutral molecule and the ion is thus shown to occur. Acrylonitrile, a radical scavenger, had no impact on the rate, excluding the idea of a free radical process. The reaction's rate constant (k) slowly decreased with an increase in [$MnSO_4$] due to the shift of two electrons. On the basis of these indications, the following process was hypothesized, and a corresponding rate rule was established.

Oxidation process and the mechanism



Scheme 1. Mechanism for the phenylic acid oxidation by PzCC

Rate equation

$$\text{Rate} = \frac{-d[PzCC]}{dt} = k_3[\text{Complex}]$$

$$= \frac{k_3K_2[S][C_1]}{1 + K_2[S]}$$

$$= \frac{k_3K_2K_1[S][PzCC][H^+]}{(1 + K_2[S])(1 + K_1[H^+])}$$

$$= \frac{k_3K_2K_1[S][PzCC][H^+]}{1 + K_2[S] + K_1[H^+]}$$

Influence of Various para and meta Substituents on the Speed of the Reaction

The reaction rate constant was determined for the substituted phenols (*meta*-Cl, *meta*-NO_2, *meta*-Br, *meta*-CH_3, *para*-CH_3, *para*-COOH, *para*-NO_2, *para*-Cl, *para*-OCH_3 and *para*-Br) at four different temperatures viz., 20^{0}C, 30^{0}C, 40^{0}C and 50^{0}C and the thermodynamic factors and activation parameters were considered from the Eyring's plot. The intermediate state of phenylic acid solvation was evidenced from the negative values of entropy of activation ($\Delta S^{\#}$) difference as specified in the Table 1. The $\Delta G\#$ values was discovered to be small, specifying that pyrazinium chlorochromate oxidised all of the substituted phenols in a coordinated manner. The linear free energy relation (LFER) is applied to a set of reactions in which the change in activation entropy is proportional to the change in activation enthalpy. The isokinetic relationship or compensation law given by Hammett relates the enthalpies at various temperature by the following equation.[16]

$\Delta H^{\#}=H_o^{\#}+S^{\#}$

The isokinetic plot between $\Delta H^{\#}$ versus $\Delta S^{\#}$ proved to be linear with r=0.956 and the isokinetic temperature (b) was 335.14 K. Low E_a values and a shift in activation enthalpy ($DH^{\#}$) point to a coordinated process. We can deduce from the linear correlation that all the meta and para substituted phenylic acids follow the identical mechanism[17]. The decline in the entropy of activation ($\Delta S^{\#}$) signifies the transition state is widely solvated owing to the amplified polarization. The following Exner relation criticized the linear correlation between $\Delta H^{\#}$ and $\Delta S^{\#}$, log (k_1) T_1=a+b log (k_1) T_2 Where T_2>T_1

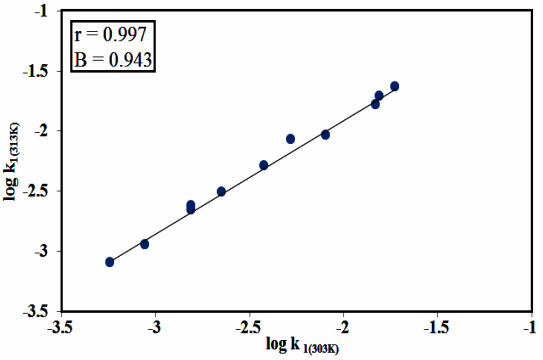


Fig. 1. Exner graph of log k_1 (313K) versus log k_1 (303K)

The plot of log $k_{1(313K)}$ versus log $k_{1(303K)}$ is undeviating with r=0.997, specifies that all the substituents show a common mechanism (Figure 1).

Table 1: Thermodynamic and Activation Limits for the Oxidation of Phenols and substituted phenols by PzCC

S. No	Substituents	Order w.r.to [S]	k_1x10^{-4} (s^{-1})Δ 293 K	303 K	313 K	323 K	$\Delta H^{\#}$ (kJ mol^{-1})	(-) $\Delta S^{\#}$ (JK^{-1} mol^{-1})	$\Delta G^{\#}$ at 303 K(kJ mol^{-1})	E_a at 303 K (kJ mol^{-1})	r
1	-H	0.667	3.73	5.93	8.17	10.81	10.92 ± 1.51	193.97 ± 2.8	69.69 ± 1.8	13.44 ± 1.51	0.995
2	*p*-Br	0.447	7.71	8.97	11.12	13.92	5.66 ± 1.49	209.52 ± 3.1	69.14 ± 1.9	8.18 ± 1.49	0.991
3	*p*-Cl	0.534	11.07	15.41	22.11	30.18	10.40 ± 1.53	191.99 ± 2.9	68.57 ± 2.1	12.92 ± 1.53	0.999
4	m-CH_3	0.528	10.72	15.80	23.12	33.79	11.97 ± 1.48	186.75 ± 2.8	68.55 ± 2.0	14.49 ± 1.48	0.999
5	m-Cl	0.597	18.12	23.37	30.39	40.69	8.06 ± 1.54	198.22 ± 3.2	68.12 ± 2.2	10.58 ± 1.54	0.998
6	*p*-CH_3	0.624	31.87	39.21	49.11	61.67	6.41 ± 1.53	201.78 ± 3.1	67.55 ± 1.9	8.93 ± 1.53	0.998
7	*p*-COOH	0.485	38.54	53.14	83.91	125.73	12.48 ± 1.46	180.50 ± 3.0	67.17 ± 1.8	14.99 ± 1.46	0.996
8	m-Br	0.497	70.68	81.63	92.54	106.94	3.58 ± 1.48	208.57 ± 2.8	66.78 ± 2.2	6.04 ± 1.48	0.998
9	*p*-NO_2	0.592	137.01	147.54	160.12	173.74	1.60 ± 1.49	212.93 ± 2.9	66.12 ± 2.1	4.12 ± 1.49	0.997
10	*p*-OCH_3	0.569	134.43	157.32	187.74	229.18	4.95 ± 1.47	201.63 ± 3.1	66.04 ± 2.2	7.47 ± 1.47	0.994
11	m-NO_2	0.380	170.51	189.49	220.12	267.79	3.54 ± 1.52	205.55 ± 3.2	65.82 ± 1.9	6.06 ± 1.52	0.991

[PzCC]=0.5x10^{-3} mol dm^{-3} [Phenylic acid]=1.5x10^{-2} mol dm^{-3} [H^+]=14.0x10^{-1} mol dm^{-3}

CH_3COOH:H_2O=60:40 (v/v)

Catalytic effect

The catalytic effect was observed from the Hammett relation of phenols with the substituent constants (β), showed non-linearity with a "V" shape curve. This implies that electron donating and electron removing substituents both speed up the reaction rate by producing negative and positive values, respectively (Table 2). This helps to confirm the involvement of electron deficient transition state in the common oxidation mechanism. The oxidation involves electron-withdrawing groups, negative charge is lost, or positive charge is produced on the intermediates.

Table 2: Catalytic effect of substituted phenols

Substituent's	ρ Δ	$k_1 x10^{-4}$ (s^{-1})	R	log k_1	Δ(Substituent constant)
para-OCH_3	-ρ(B=-5.1174) (r=0.9964)	157.32	0.988	-1.8032	-0.27
para-CH_3		39.21	0.994	-2.4066	-0.17
meta-CH_3		15.80	0.990	-2.8013	-0.07
-H		5.93	0.991	-3.2269	0.00
-H	+ρ(B=+2.047) (r=0.940)	5.93	0.991	-3.2269	0.00
para-Br		8.97	0.998	-3.0470	0.23
para-Cl		15.41	0.990	-2.8122	0.23
meta-Cl		23.37	0.999	-2.6313	0.37
para-COOH		53.14	0.984	-2.2746	0.45
meta-Br		81.63	0.998	-2.0882	0.39
para-NO_2		147.54	0.993	-1.8311	0.78
meta-NO_2		189.49	0.991	-1.7224	0.71

The Hammett Plot of Non-Linearity

The Hammett constant (σ) and reaction rate constant (k_1) for the *para-* and *meta*-substituted phenols produced a "V" shaped, upward curve (Fig. 2) with a positive slope value. The variation in the slow step is due to the nature of the substituted group in phenol and nature of the intermediate state is the main reason for non-linearity in Hammett plot. The electron contributing groups was lined up on one side of the curve and the electron accommodating groups fall on the other side of the curve.

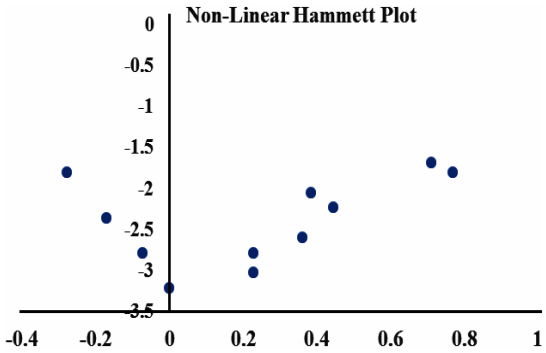


Fig. 2. Non-Linear Hammett Plot of log k_1 versus σ

Evaluation of antibacterial activity

Pyrazinium chlorochromate's antibacterial activity was tested using the well diffusion technique on Mueller-Hinton agar (MHA). The microorganisms were collected from Trichy Analytical Lab and Research Institute (Eumic). Some bacteria like *Proteus vulgaris, Streptococcus, Entrococcus, Micrococcus, Bacillus cereus, Mycobacterium tuberculosis*, and fungi like *Trichoderma*, *A. niger, Candida albican* and, *Fusarium*, were used as references for the antibacterial assay of the oxidant. Mueller-Hinton agar plates were inoculated with bacterial strain under sterile condition and wells of diameter (6mm) were filled with 25 µL to 100 µL in DMSO of the test samples (PzCC) and incubated at 37°C for 25 to 28 hours. The diameter of the inhibitory zone growth was assessed after the incubation time. Single colonies on agar plates were grown for 18 to 24 h to produce a bacterial solution with a turbidity of 0.5 McFarland (equivalent to 1.5x108 colony-forming units (CFU)/mL)[18,19]. The control was Ciprofloxacin, a common antibiotic. In the case of *Gram-positive* strains of *Mycobacterium tuberculosis* (20 mm/mL), the compound PzCC showed good impedance, which was comparable to the control, and the inhibition of *Proteus vulgaris* (25 mm/mL) was larger than that of Ciprofloxacin as specified in the Figure 3.

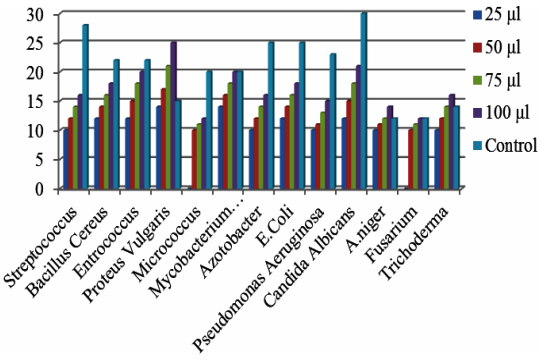


Fig. 3. Inhibition Zone for Pyrazinium Chlorochromate (PzCC)

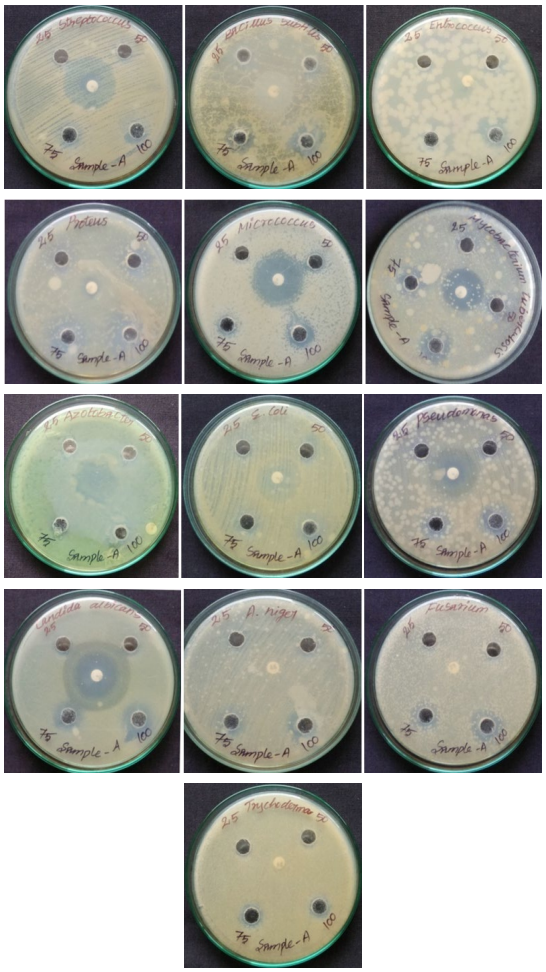


Fig. 4. Agar well diffusion method-Inhibition zone for P3zCC

CONCLUSION

The investigation of oxidation reaction mechanism of phenol using pyrazinium chlorochromate proved the order followed first order kinetics for [O], fractional order for the [S] and [H^+]. The rate of reaction did not vary as the medium's ionic strength increased. Though the ionic strength contributed by the [$NaClO_4$] of the reaction medium was raised, the reaction speed remained unchanged. With a drop in the medium's dielectric constant (D), the reaction rate increased. When acrylonitrile was added, the free radical process was not detected. The presence of Mn(II) ions in the oxidation response was demonstrated by the addition of manganous sulphate. The activation and thermodynamic parameters $\Delta H^{\#}$, $\Delta S^{\#}$, $\Delta G^{\#}$ and E_a were evaluated for all the substituted phenols under investigation. The isokinetic plot ($\Delta H^{\#}$ versus $\Delta S^{\#}$) showed linearity with r=0.956 and the isokinetic temperature (β=335.14 K) and non-linearity in the Hammett plot was evidenced from the reaction mechaism and the rate law. The antibacterial studies for the prepared compound exhibited higher resistance to few *Gram-positive* bacteria such as *Entrococcus* (20 mm/mL), *Mycobacterium tuberculosis* (20 mm/mL) *Gram-negative* bacteria *E.coli* (18 mm/mL) and for the fungi *A. niger* (14 mm/mL) and *Trichoderma* (16 mm/mL) respectively.

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