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Kinetics of oxidation of substituted 2-phenylthiazolidines by pyridinium chlorochromate

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Kinetics of oxidation of 2-phenylthiazolidine (PT) and substituted PT (SPT) by pyridinium chlorochromate (PCC) in dry acetic acid have been investigated. The reaction is first order in PCC and fractional order in PT and it exhibits Michaelis-Menten kinetic character. The complex formation constants (K) and the decomposition rate constants (k_1) have been computed from the double reciprocal plots of $1/k_{obs}$ versus $1/[PT]_0$. The decomposition rate constants are not correlated by Hammett σ constants. Nevertheless, they show satisfactory correlation with σ_I and σ_R parameters. The correlation with Swain and Lupton F and R values is relatively less satisfactory.

The saturated heterocyclic thiazolidine ring system forms part of medicinally important compounds like penicillin. Very diverse range of biological activities like bactericidal, fungicidal and antiinflammatory activities are associated with thiazolidine derivatives. The cysteinyl peptides are synthesised through thiazolidine intermediates which act as an effective protecting group for both amine and thiol functionalities[1]. The most pronounced biological activity of PT and SPT is their antiradiation property[2]. The thiazolidine ring is very sensitive to oxidation by peroxydisulphate and bromate ions[3]. However, we find that PCC oxidises this ring system very smoothly and that it has been possible to obtain satisfactory kinetic results. There is no evidence of any systematic investigation in the literature on the kinetics of oxidation of PT and SPT. Hence, the title work is undertaken with a view to seek structure-reactivity correlation in SPT.

Materials and Methods

PCC was prepared by the method of Corey and Suggs[4] as modified by Agarwal *et al*[5]. All the SPT were prepared by Tsukerman's general procedure[6]. Other chemicals used were of AnalaR grade. AnalaR acetic acid was further purified by literature method.

Rate measurements

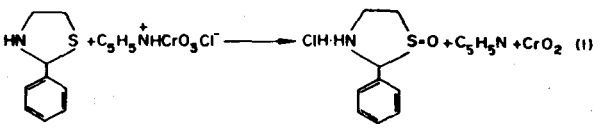
The kinetics of oxidation of substituted PT by PCC were followed at three different temperatures in dry acetic acid under pseudo-first order condition, keeping $[PT]_0 \gg [PCC]_0$. The kinetics were followed by monitoring the decrease in the absorption of PCC at 356 nm in a UVIDEC-340 spectrophotometer.

Product analysis

PT and PCC were mixed in the same proportion as used in the kinetic measurements and kept at 30°C overnight. The product was isolated by repeated extraction with 1:1 carbon tetrachloride-chloroform and purified by crystallization from aqueous methanol. The product melted at 302-304°C. The elemental analysis, ^1H NMR and IR data showed that the isolated product was the hydrochloride of 2-phenylthiazolidine-1-oxide.

Stoichiometry

The estimation of unreacted PCC establishes 1:1 stoichiometry and thus the oxidation is believed to proceed according to Eq. (1) involving two electron transfer[7-9].



Results and Discussion

The reaction is first order in PCC as seen from the linearity of log optical density versus time plot over 75% of the reaction. There is no variation in the observed pseudo-first order rate constant at a fixed $[PT]_0$ when $[PCC]_0$ is varied (Table 1). The plot of log k_{obs} versus log$[PT]_0$ is linear with a slope < 1 for all the SPT. This shows that the or-

der in SPT is fractional. At constant $[PCC]_0$, k_{obs} increases with increase in $[PT]_0$. The double reciprocal plot of $1/k_{obs}$ versus $1/[PT]_0$ for the oxidation of PT by PCC in acetic acid at 30°C is linear with a definite intercept (Fig. 1). This indicates that the reaction in acetic acid follows Michaelis-Menten kinetics[10] with the formation of a complex prior to the rate-limiting step. From the plots, the complex formation constants (K) and the complex decomposition rate constants (k_1) were evaluated for all SPT. The k_{obs} at three different temperatures and at a definite concentration of SPT are presented in Table 2 and those observed at varying concentrations of SPT are presented in Table 3. The decomposition rate constants (k_1) and the complex formation constants (K) evaluated for different SPT are given in Table 4. The activation parameters are also recorded in Table 4.

Table 1—Pseudo-first order and second-order rate constants for the oxidation of PT by PCC in dry acetic acid at 30°C.

$10^4[PCC]_0$ (mol dm^{-3})	$10^3[PT]_0$ (mol dm^{-3})	$10^3\,k_{obs}$ (s^{-1})	k_2 ($dm^3mol^{-1}s^{-1}$)
10.0	20.0	13.03	0.65
9.1	20.0	13.29	0.66
8.1	20.0	13.27	0.66
7.1	20.0	13.82	0.69
4.2	5.0	11.12	2.24
3.2	5.0	11.56	2.33
2.5	8.1	12.62	1.56
2.5	7.0	12.37	1.76
2.5	6.0	11.54	1.91
2.5	4.1	10.73	2.64

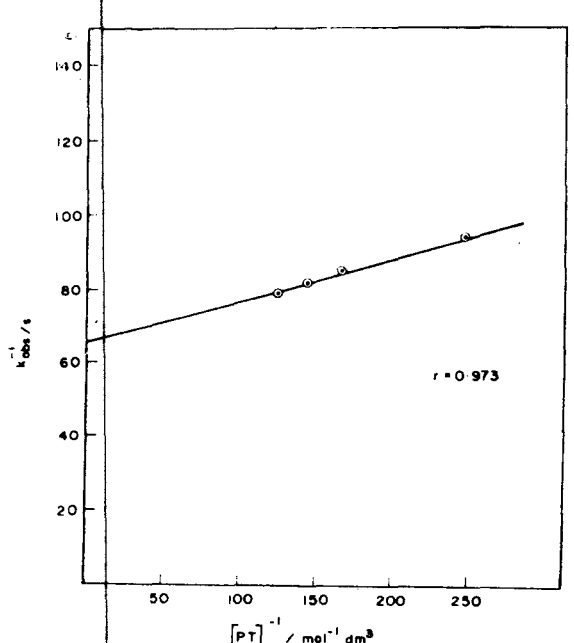


Fig. 1—Michaelis-Menten plot for the oxidation of PT by PCC in acetic acid at 30°

Mechanism and rate law

The $\Delta S^{\neq}$ values are not constant within the series. But they are linearly related to the $\Delta H^{\neq}$ providing $\beta = 304$ K. This linearity between $\Delta S^{\neq}$ and $\Delta H^{\neq}$ is indicative of constant mechanism. Other observations suggest that the reaction may follow the mechanism in Scheme 1, in which there is a reversible formation of a complex followed by its irreversible slow decomposition.

$$PT + PCC \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} PT.PCC\ (Complex)$$

$$Complex \xrightarrow{k_1} Product + Cr(IV)$$

Scheme 1

Table 2—Pseudo-first order rate constants for the oxidation of SPT by PCC in dry acetic acid

$[SPT]_0 = 0.0090$ mol dm^{-3}; $[PCC]_0 = 0.00090$ mol dm^{-3}

Substituent	$10^3\,k_{obs}$ (s^{-1})		
	20.1°	25.5°	30.0°C
m-Br	14.26	18.30	23.83
p-Cl	12.88	15.57	19.88
p-Br	11.48	14.63	17.39
H	11.12	13.27	16.67
m-CH_3	9.59	11.11	14.64
m-NO_2	5.19	6.80	8.61
p-CH_3	3.14	4.53	6.83
p-NO_2	3.06	3.60	4.19
p-OCH_3	2.53	3.20	3.79
m-OH	1.77	2.56	3.07

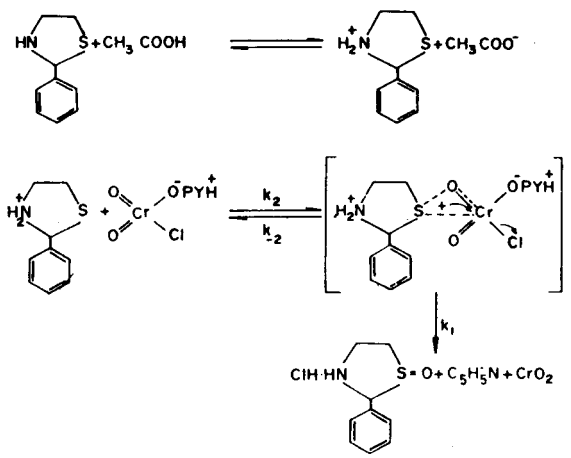
Table 3—Pseudo-first order rate constants for the oxidation of SPT at various initial concentrations by PCC in dry acetic acid.

In I, $[SPT]_0 = 0.0080$ mol dm^{-3}; in II, $[SPT]_0 = 0.0070$ mol dm^{-3}; in III, $[SPT]_0 = 0.0060$ mol dm^{-3} and in IV, $[SPT]_0 = 0.0041$ mol dm^{-3}; $[PCC]_0 = 0.00025$ mol dm^{-3} at 30°C.

Substituent	$10^3\,k_{obs}$ (s^{-1})			
	I	II	III	IV
m-Br	19.25	18.08	16.01	15.01
p-Cl	17.13	16.42	15.47	14.54
p-Br	13.94	13.31	12.63	11.49
H	12.62	12.37	11.54	10.73
m-CH_3	14.13	13.56	13.34	12.41
m-NO_2	4.94	4.24	3.48	2.84
p-NO_2	2.30	2.07	1.64	1.44
p-CH_3	5.16	4.86	4.57	4.24
p-OCH_3	2.16	2.08	1.97	1.84
m-OH	1.51	1.37	1.18	1.05

Table 4—Decomposition rate constants (k_1), equilibrium constants (K) and activation parameters for the oxidation of SPT by PCC [SPT] = 0.0080 mol dm^{-3}; 0.0070 mol dm^{-3}; 0.0060 mol dm^{-3}; 0.0041 mol dm^{-3}; $[PCC]_0 = 0.00025$ mol dm^{-3}

Substituent	$10^3 k_1$ (s^{-1})			K_{303} (dm^3 mol^{-1})	E_a (KJ mol^{-1})	$\Delta H^{\ddagger}_{303}$ (KJ mol^{-1})	$-\Delta S^{\ddagger}_{303}$ (JK^{-1} mol^{-1})
	20.1°	25.5°	30.0°C				
m-Br	21.55	24.31	25.11	362.00	12.4	9.9	243.1
p-Cl	16.49	17.42	20.22	610.62	15.4	12.8	235.2
p-Br	10.28	12.97	17.47	440.38	39.8	37.3	155.8
H	7.81	12.01	15.23	597.00	50.8	48.3	120.5
m-CH_3	10.02	13.27	16.06	830.13	36.6	34.1	166.9
m-NO_2	6.78	7.31	14.26	59.95	54.2	51.7	109.9
p-CH_3	2.83	3.43	6.29	497.00	59.9	57.3	98.0
p-NO_2	3.50	3.92	4.67	105.93	22.4	19.9	224.1
p-OCH_3	1.68	1.93	2.55	621.14	30.9	28.4	201.0
m-OH	1.40	1.85	2.41	184.41	40.0	37.5	171.6



Scheme 2

By applying steady state approximation to the complex, Eq. (2) is obtained for the observed kinetics.

$$1/k_{obs} = 1/Kk_1[PT]_0 + 1/k_1 \quad \ldots(2)$$

In acid medium thiazolidine exists in its protonated form which reacts with PCC as shown in Scheme 2.

Scheme 2 envisages an oxygen atom transfer from the oxidant and this is in line with the earlier observations made in the oxidation of sulphides by PCC[7,8]. There is a transfer of an electron in the first step which is followed by unimolecular decomposition of the ion-pair due to the transfer of the second electron. There is no systematic influence of substituents on K, the complex formation constant. However, certain values of K indicate that electron-donating substituents generally stabilise the complex and favour the formation of the complex which results in high K values in most cases and the electron-withdrawing substituents do not favour much the formation of the complex resulting in decrease of K values.

It is interesting that there is no regularity in k_1 values in respect of substituent effect. The Hammett plot of log (k_1/k_1^0) versus σ is not linear with $r = 0.305$ at 30°C. A similar correlation with σ_I is insignificant with $r = 0.199$ at 30°C. The single parameter equations fail to predict the reactivity. Hence, the rate data were analysed in terms of Taft's[11] and Swain's[12] dual substituent parameter equations (3) and (4) respectively.

$$\log k_1 = \rho_I\sigma_I + \rho_R\sigma_R + h \quad \ldots(3)$$
$$\log k_1 = fF + rR + h \quad \ldots(4)$$

where σ_I and σ_R are inductive and resonance parameters respectively and F and R are non-resonance and resonance parameters respectively.

Application of Eq. (3), to all the substituents generates Eqs (5-7) at 20.1, 25.5 and 30.0°C respectively.

$$\log k_1 = 0.8076 + 0.2878\sigma_I + 0.5640\sigma_R \quad \ldots(5)$$
$$(\pm 0.4778)(\pm 0.5410)$$
$$R = 0.403;\ s = 0.420;\ n = 10;\ SL < 90\%$$

$$\log k_1 = 0.9362 + 0.1625\sigma_I + 0.5732\sigma_R \quad \ldots(6)$$
$$(\pm 0.4787)\ (\pm 0.5421)$$
$$R = 0.380,\ s = 0.421;\ n = 10;\ SL < 90\%$$

$$\log k_1 = 1.9022 + 0.1522\sigma_I + 0.6800\sigma_R \quad \ldots(7)$$
$$(\pm 0.4298)\ (\pm 0.4867)$$
$$R = 0.472;\ s = 0.378;\ n = 10;\ SL < 90\%$$

As such Eqs (5-7) do not predict the reactivity satisfactorily. However, when *p*-NO_2 and *m*-NO_2 groups are excluded, the correlation obtained is quite satisfactory as in Eqs (8-10) at 20.1, 25.5 and 30.0°C respectively.

$$\log k_1 = 0.9428 + 1.7992\sigma_I + 1.9453\sigma_R \quad \ldots(8)$$
$$(\pm 0.3908)\ (\pm 0.3898)$$
$R = 0.923$; $s = 0.206$; $n = 8$; $SL > 99\%$

$$\log k_1 = 1.0718 + 1.6784\sigma_I + 1.9586\sigma_R \quad \ldots(9)$$
$$(\pm 0.3950)\ (\pm 0.3941)$$
$R = 0.918$; $s = 0.208$; $n = 8$; $SL > 99\%$

$$\log k_1 = 1.2126 + 1.4990\sigma_I + 1.9108\sigma_R \quad \ldots(10)$$
$$(\pm 0.2753)\ (\pm 0.2746)$$
$R = 0.954$; $s = 0.145$; $n = 8$; $SL > 99\%$

Our crystal structure studies[13] of *m*- and *p*-SPT indicate that the benzene ring is nearly perpendicular to the thiazolidine ring and the disposition of the *meta*-nitro group is such as to sterically prevent to some extent the approach of the oxidant. While this may explain why the correlation is poor with this substituent, it is not clear why only after the removal of *para*-nitro group the correlation was better. However, one possible explanation for the deviation of *para*-nitro group may lie in the group making an angle of 4.99° with the least squares plane of the phenyl ring. From this, it may be inferred that PCC experiences a steric crowding in the transition state while approaching the *p*-NO_2 compound. This may be the reason for the departure of the *p*-NO_2 group from linearity.

Application of Eq. (4), even after excluding *m*-NO_2 and *p*-NO_2 groups is not as successful as with Eq. (3), and it generates Eqs (11-13) at 20.1, 25.5 and 30.0°C respectively.

$$\log k_1 = 0.9879 + 1.2101F + 2.0348R \quad \ldots(11)$$
$$(\pm 0.4390)\ (\pm 0.6442)$$
$R = 0.878$; $s = 0.235$; $n = 7$; $SL < 98\%$

$$\log k_1 = 1.1283 + 1.0841F + 2.1600R \quad \ldots(12)$$
$$(\pm 0.4307\ (\pm 0.6321)$$
$R = 0.882$; $s = 0.230$; $n = 7$; $SL \leq 98\%$

$$\log k_1 = 1.2640 + 0.8858F + 2.0635R \quad \ldots(13)$$
$$(\pm 0.3098)\ (\pm 0.4546)$$
$R = 0.923$; $s = 0.166$; $n = 7$; $SL > 99\%$

The composition of electronic effect was calculated using Eq. (14), as applicable to Eq. (10). The resonance contribution is 56%. This suggests that the non-resonance effect is of equal importance as the resonance effect in the present investigation.

$$P_R = (\beta \times 100)/(\alpha + \beta) \quad \ldots(14)$$

where α and β are the weighting factors of inductive or non-resonance and resonance effects respectively.

The significance attached to $R = 0.954$ as obtained from Eq. (10) is that 95% of the variation in $\log k_1$ is explained by σ_I and σ_R. The coefficient of σ_I is significant at 1% level of probability.

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