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Kinetics and mechanism reaction of hydrolysis of mono-4-chloro, 3-methyl phenyl phosphate ester in acidic medium

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Abstract

Kinetics and mechanism of and hydrolysis of mono-4-chloro, 3- methyl phenyl phosphate has been carried out in the pH range, 1.24 to 7.46 in aq. dioxin media at 97±0.5.^{0}C Neutral species although shown to be present by salt effect study. Which does not seem to participate in the reaction at the lowest pH value 1.24 examined. Mononegative species, however, in the pH region upto 7 gets hydrolysed unimolecularly. This is also evident from the low entropy value, isokinetic relationship ($\beta = 333.3^0K$) and solvent effect studies and thus lends strong support for the intramolecular general acid catalysis by the hydroxyl group of the monoanion. The dinegative species is rather inert between pH 4 and 7. Its contribution to the overall rate becomes significant after pH 7. The reactivity depends largely upon the highly basic nature of the leaving group caused by +m effect of three halogen substituents. $pK_1$and pK_2 values have been determined to be 1. 17 and 6.8 respectively. The monoester and the parent compound have also been tested for their antifungal activity.

Keywords: kinetics, hydrolysis, mono-4-chloro, 3- methyl phenyl prosphate ester

Introduction

Present investigation on the kinetics and mechanism of hydrolysis of mono-4-chloro, 3- methyl phenyl phosphate esters. Later work from our Research Laboratory Department of Chemistry Agra College, Agra included the study of the kinetics of hydrolysis of sym-halo-substituted phenyl orthophosphates [1].The work has been undertaken with a view to finding out the effect of 0-Cl subsituent on the rate of hydrolysis as well as the antifungal activity of the phosphate ester. The present study mainly deals to like the similar work [2, 3] has been carried out in a wide pH range 1.24 to 7.46. Recently the kinetic study of hydrolysis has been carried out by various Workers [4, 5].

Materials of Methods

Compound mono-4-chloro, 3- methyl phenyl phosphate and $POCI_3$ in the ratio of 1:5 were refluxed together for 12 hr in the presence of KCI (0.1g). The chloridate so formed was hydrolysed to free ester which on treatment with cyclohexylamine gave a white precipitate of the corresponding salts. The salt was recrystallised from rectified spirit, m.p. 184^0. (Found: C, 35.91; H, 4.09: P, 7.67; N, 3.36. Calc. for $C_{12}H_{17}PO_4N$: C, 37.81; H, 4.46; P, 8.14; N, 3.68%).

Kinetics and mechanism of hydrolysis of mono 4-chloro, 3-methyl phenyl phosphate has been investigated in the pH range 1.24-7.46 at 97±0.5^{0}C. The progress of the reaction was followed by estimating the rate of appearance of inorganic phosphate [6]. Buffers required for pH adjustments were employed as cited in different sources [7, 8]. Concentration of the monoester was maintained at 5x10^{-4} mol dm^{-3} throughout the study.

Results and Discussion

The first order rate constants for the hydrolysis of Mono-4-chloro, 3- methyl phenyl phosphate increase with the increase in pH upto 4.17 and thereafter the rate constants decrease and results are shown in Table-1. This can be attributed to the incursion of highly reactive monoanion of the monoester, which is formed maximally at pH 4.17. Two dissociation constants (pK_1 and pK_2) are derived from Equation (1) and (2) by assuming the observed rate at pH 4.17 to be equal to the specific rate (k_{m0}=5.31x 10^{-3} min^{-1}) of hydrolysis of mononegative species ($\approx 99.99\%$)

$$N \overset{K_1}{\Rightarrow} M+H^+ \qquad \text{……(1)}$$

$$M \overset{K_2}{\Rightarrow} D+H \qquad \text{……..(2)}$$

In Equation (1) and (2) N, M and D stand for the neutral, mononegative and dinegative species of the monoester respectively. From these pK values (pK_1=1.17and pK_2=6.8), fractions of mononegative (M/N+M) as well as dinegative (D/M+D) species present at different pH values has been calculated. Since the rates are proportional to the concentration of individual reactive species, the total rates due to mononegative (K_m) as well as dinegative (k_D) species can be given by Equation in (3-5) as follows

$$ke_{calc} = k_m + k_D \qquad \text{………(3)}$$

$$k_M = k_{Mo} M/N_{+M} \qquad \text{………(4)}$$

$$k_D = k_{Do.} D/M_{+D} \qquad \text{…..…..(5)}$$

Where, k_{Mo} and k_{Do} are the specific rate coefficients for the singly ionised and doubly ionised species respectively.

Table 1: Rate Coeffcients for the Hydrolysis of mono 4-chloro, 3- methyl phenyl phosphate at 97±0.5^{0}C

S. No.	pH	M/N+M	103 km (min-1)	103kecalc (min-1)	103keobs (min-1)	(min-1)	(min-1)
1.	1.24	0.540	2.87	-	-	2.87	3.31
2.	1.61	0.733	3.89	-	-	3.89	3.75
3.	2.20	0.914	4.85	-	-	4.85	4.02
4.	2.50	0.955	5.07	-	-	5.07	4.25
5.	3.33	0.993	5.27	-	-	5.27	4.77
6.	3.70	0.997	5.29	-	-	5.29	5.08
7.	4.00	0.999	5.30	-	-	5.30	5.17
8.	4.17	0.999	5.30	-		5.30	5.31
9.		M/N+M		D/D+M	-		
10.	5.10	0.981	5.21	0.019	-	5.21	4.42
11.	5.60	0.944	5.01	0.056	-	5.01	4.05
12.	6.43	0.712	3.78	0.288	-	3.78	3.35
13.	7.46	0.188	1.00	0.812	0.89	1.89	2.33

Table 2: Comparative Kinetic Study for the Hydrolysis of Halogen-subsituted phenyl phosphates Mononegative Species.

S.No.	Monoesters	10^3 k_m (min^{-1})	Temp ^{0}C	Maxima at pH	E.K. cal. Mol	$-\Delta S^\ddagger$ K^{-1} mol^{-1} (E.U.)	Bond Fission
1.	Phenyl	32.00	97	-	27.46	241.5	P-0
2.	B-Napthyl	54.20	96	4.17	30.48	157.4	P-0
3.	Bombanide	1.36	80	4.11	27.48	243.4	P-0
4.	2-Cloro-4-Nitro	14.74	97	4.17	19.90	158.1	P-0
5.	2,-di, methyl phenyl	25.71	97	4.17	17.84	134.3	P-0
6.	2,4,di,Chloro phenyl[1,20]	0.02	90	-	17.46	102.1^n	P-0
7.	4 T^6-di-methyl phenyl	5.31	90	4.17	14.14	236.1^b	P-0

Where a and b parameters at 0.1 dm^3 mol^{-3} of (ester) and at pH 1.24 respectively.

At pH 1.24 the rate of hydrolysis of neutral species, (ke= 2.78 x 10^{-3} min^{-1}), which is the same as that obtained from salt effect, i.e. k_{No}=2.69 x 10^{-3}min^{-1}, is somewhat lower than that due to the monoanion (ke_{calc}=2.82 x 10^{-3} min^{-1}). The little difference between observed and calculated rates may be attributed to the presence of neutral form (~46%). The neutral electrolyte effect study (not included) in acid shows the presence of neutral form in the entire acid range. The critical value is thus obtained at pH 1.24 and monoanion is taken to be contributing as it is present in excess (>50%). The rates thus calculated via monoanion species (Eq.4) only, agree with the observed rates upto pH 7 nearly (Table-1). Monoanion [9] of the monoster (ke=5.31 x 10^{-3} min^{-1} at pH 4.17) is found to be nearly 6 times more reactive than that of the diester (ke=0.94 x 10^{-3} min^{-1} at pH 5.1) of the same series. Such a reactivity difference can be attributed to a variety of hydrogen-bonded [10] structures that could be formed with water. An intramolecular hydrogen-bonded structure has been suggested to account for the reactivity of the monoanion of this monoester. The low entropy value [11] (Table 2) also favours a pathway, which does not require a water molecule in the transition state. Thus the hydrolysis of the monoester via its monoanion form is mainly governed by entropy factor, which is further supported by isokinetic relationship ($\beta = 333.3^0K$,) being lower than the experimental temperature). The formation of four center transition state[1] is also strengthened by examining the hydrolysis in solvent of high proton-donating [9] ability like dioxin-water. The data in Table -3, reveal that a change over from 16% dioxin to 83% brings about nearly two-fold increase in the rate of hydrolysis of the monoester. This can be accounted for by the partial protonation of the oxygen atom of the leaving group, leading the conversion of the sole monoanion into its transition state. At pH 1.24 too, the rates are enhanced as we go from aqueous to 16% aq. dioxan Medium (Table-3). Further increase in percentage of dioxan, i.e. 64% and 83% aq. Dioxin, decreases the rates at pH 1.24 (Table-3). This can be attributed to the stabilization of monoanian from of the monoester by hydrogen-bonding (Structure A or B) between o-halogen (-CI-) and the –ve oxygen, by the proton of the solvent, thereby decreasing the total rate of hydrolysis. Also increase in percentage of dioxan might result in the conversion of the monoanion into the neutral form, the letter being almost non-contributary. Beyond pH 4.17, the decrease in rate may be attributed to the incursion of less reactive dianion of the monoester. However, calculated rates (Table 1) require the participation of only mononegative species upto pH 7 nearly. Thus dinegative species of the monoester does not contribute between pH 4.17 and 7. Beyond pH 7 dinegative species (>80%) however, predominates upto pH 7.46. The rates Calculated as well as dinegative species between pH 4.17 an 7.46 are still found to differ from observed rates. The dinegative species in phosphate esters has been found to undergo hydrolysis unimolecularly [12]. and its reactivity depends upon the basis nature of the leaving group rather Then the nucleophilicity of the attacking reagent. The unimolecular route of hydrolysis for the dinegative species of the present monoester is more likely because the steric effect of an o-CI substituent and –ve charge on the oxygen atoms of the dianion will hinder the approach of the nucleophile, the OH^- ions, to the reaction centre in the higher pH range. Also the substituted phenoxide ion to be formed will be further aided by the +M effects of the two halogens which make it to be strongly basis leaving group.

Table 3: Influence of Solyent Polarity & Temperature on the rate of Hydrolysis of mono 4-chloro, 3- methyl phenyl phosphate at $97\pm0.5C^0$.

S. No.	pH	Dioxan (%)	10^3ke_{obs} (min^{-1})
1.	1.24	0	3.31
2.	1.24	16	4.22
3.	1.24	64	2.07
4.	1.24	83	1.84
5.	4.17	0	5.31
6.	4.17	16	7.25
7.	4.17	83	12.55

a and b = 10^3 ke min^{-1} at 80^0 and 97^0C respectively.

Isokinetic relationship [13] ($\beta = 333.3K$) and comparative kinetic data (Table 2) suggest the P-O bond rupture as is prevalent in other monoaryl phosphate esters. P-O bond rapture is also expected due to the formation of stable halogen-substituted phenoxide ions.

Many halogen-subsituted phenols have been reported to display antifungal activity. Considering this fact, an attempt has been made to assess how the mixed halogen-substituted phenyl system when present as such or attached to the phosphoryl group, affects this activety. In order to determine this aspect, mono 4-chloro, 3- methyl phenyl phosphate and its corresponding phenol were tested *in vitro* for their antifungal activity against four strain of dermatophytes, *viz T. mentagropyhtes, T. rubrum, M. gypseum and E. floccosum* using streak agar technique [12,13]. Dimethylformamide (2%) was used as a diluents for the dissolution of test compounds.

Mono-4-chloro, 3- methyl phenyl exhibits profound activity against all the four strains of dermatophy examined. Mono 4-chloro, 3- methyl phenyl phosphate on the other hand, shows no inhibitory effect against T. mentorgrophytes and M. gypseum even in concentrations upto $\mu g/ml$. T. rubrum and E. floccosum are, however, found to be sensitive towards the monoester at a concentration of 25 $\mu g/ml$. The decrease in the antifungal activity of the monoester indicates the retarding influence of the phosphate.

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