



KINETIC STUDY OF HYDROLYSIS OF DI-3-CHLORO-2-METHYLANILINE PHOSPHATE IN ACID MEDIUM

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ABSTRACT

Kinetic study of the hydrolysis of di-3-chloro-2-methyl aniline phosphate has been carried out in the acid region, 0.5 to 7.0 mol dm⁻³ HCl at 80°C in 40% (v/v) dioxane-water medium. The rate of hydrolysis increases with increase in acid molarity up to 4.0 mol dm⁻³ HCl and after that it decreases. The lowering of rate after 4.0 mol dm⁻³ HCl has been attributed to the effect of water activity. Ionic strength data is used to identify reactive species and find out theoretical rates. Bimolecular behaviour of the hydrolytic reaction has been decided by Arrhenius parameters, Hammett acidity function, Zucker Hammett equation, Bunnett and Bunnett-Olsen parameters. Solvent effect on hydrolytic reaction has been found to indicate the formation of a transition state in which charge dispersion occurs.

Key words: Hydrolysis, Di-3-chloro-2-methyl aniline phosphate, Ionic strength.

INTRODUCTION

Organic phosphates have found a broad range of applications in the areas of industrial, agricultural and medicinal chemistry owing to their biological and physical properties, as well as their utility as synthetic intermediates¹. Many multi-ring phosphorus heterocycles are used as pesticides², bactericides^{3,4}, antibiotics⁵ and act as HIV protease inhibitors⁶. Phosphate esters have also achieved importance in industry as solvent and as fuel additives for explosion control. These esters are also used as additives in the textile and clothing dyeing industry⁷. The hydrolysis of phosphate esters is one of the most fundamental chemical and biochemical reaction⁸. Reaction at the phosphorus atom of phosphate esters and anhydrides form the chemical basis for many of the most fundamental process in living system⁹. In the biochemistry of living organisms, there are many kinds of monophosphate, diphosphate and triphosphate compounds (essential esters) and of these, many have significant role in metabolism such as adenosine diphosphate (ADP) and adenosine

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triphosphate (ATP)¹⁰. Phosphate ester transformation being a metabolic process appreciated biochemists as well as physic-organic chemists, to study the complexity and variety of mechanistic aspect of the ester reaction¹¹.

EXPERIMENTAL

Di-3-chloro-2-methyl aniline phosphate was synthesized by the Rudert method¹² in our laboratory, which involves the reaction of 3-chloro-2-methyl aniline with phosphorylating agent phosphorus oxychloride in 2:1 mol ratio which gave crude diester as a solid. The crude product so obtained was recrystallized by ammonia and HCl to get pure sample. Hydrolysis of di-3-chloro-2-methylaniline phosphate was carried out at 80°C by employing 5.0×10^{-4} mol dm⁻³ solution in 40% (v/v) dioxane–water medium. The progress of hydrolysis was studied spectrophotometrically by Allens modified method¹³ at 735 nm. The confirmation of compound was done by elemental and IR spectrum analysis.

- (a) Elemental analysis (%); calculated (observed): C, 47.9 (38.3); H, 6.0 (5.7); N, 7.9 (7.4).
- (b) IR absorption spectrum: The spectrum of di-3-chloro-2-methylaniline phosphate was recorded by FTIR Model 136 Shimadzu. ν (KBr) (cm⁻¹): 3050.00 (N-H); 3405.54 (O-H); 1574.05 (C=C); 1263.15 (P=O); 779.38 (P-N); 2901.21 (C-H).

RESULTS AND DISCUSSION

Hydrolysis via conjugate acid species

The kinetics of the hydrolysis of di-3-chloro-2-methyl aniline phosphate was studied in 0.5-7.0 mol dm⁻³ HCl in 40% (v/v) dioxane-water medium at 80°C. The pseudo-first order rate constants were obtained. These are summarized in Table 1 and illustrated by Fig. 1.

Table 1: Rate data for the hydrolysis of di-3-chloro-2-methylaniline phosphate ester

S. No.	HCl (mole dm ⁻³)	$k_e \times 10^3$ (min ⁻¹)	$3 + \log k_e$
1	0.5	10.67	1.03
2	1.0	15.55	1.19
3	1.5	20.46	1.31
4	2.0	27.76	1.44

Cont...

S. No.	HCl (mole dm ⁻³)	$k_e \times 10^3$ (min ⁻¹)	$3 + \log k_e$
5	2.5	36.89	1.57
6	3.0	45.40	1.66
7	3.5	63.74	1.80
8	4.0	76.36	1.88
9	5.0	56.77	1.75
10	6.0	38.17	1.58
11	7.0	16.44	1.22

Conditions: [Substrate] = 5.0×10^{-4} , Temperature = 80°C.

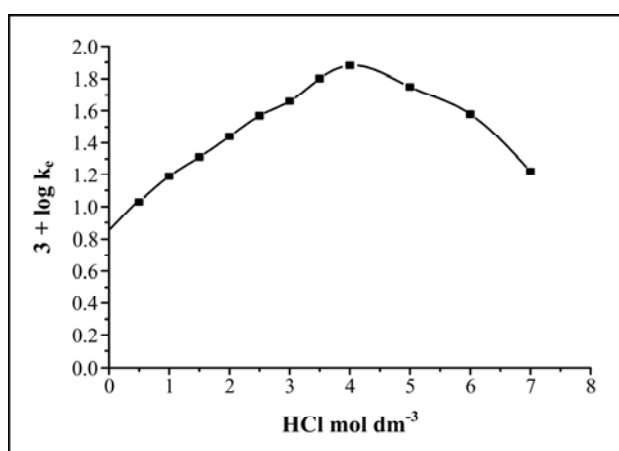


Fig. 1: Plot of $3 + \log k_e$ versus HCl mol dm⁻³ for the hydrolysis of di-3-chloro-2-methylaniline phosphate

From the results, it may be seen that the rate of reaction increases with increase in acid molarity up to 4.0 mol dm⁻³ HCl. The maximum rate at 4.0 mol dm⁻³ HCl was attributed to complete conversion of the substrate into its conjugate acid species as described in Scheme 1. The decrease in the rate after 4.0 mol dm⁻³ HCl was attributed to the lowering of concentration of attacking nucleophile taking part in the reaction, i.e., due to variation in water activity.

Effect of ionic strength

The kinetic salt effect was studied at six different ionic strength from 0.5 to 3.0 μ , using an appropriate mixture of hydrochloric acid and sodium chloride. Hydrolysis at

constant ionic strength shows that the reaction proceeds via both neutral and conjugate acid species. The plot of rate constants against acid molarity at each ionic strength is linear Fig. 2. Six linear curves are obtained and each represents the hydrolysis at that ionic strength. Linear plots show the acid-catalysed hydrolysis of di-3-chloro-2-methylaniline phosphate at different ionic strengths by following rate equation:

$$k_e = k_{H^+} \cdot C_{H^+} \quad \dots(1)$$

Where k_e , k_{H^+} and C_{H^+} are experimental rate constant, specific acid catalysed rate at that ionic strength, and concentration of H^+ ion, respectively.

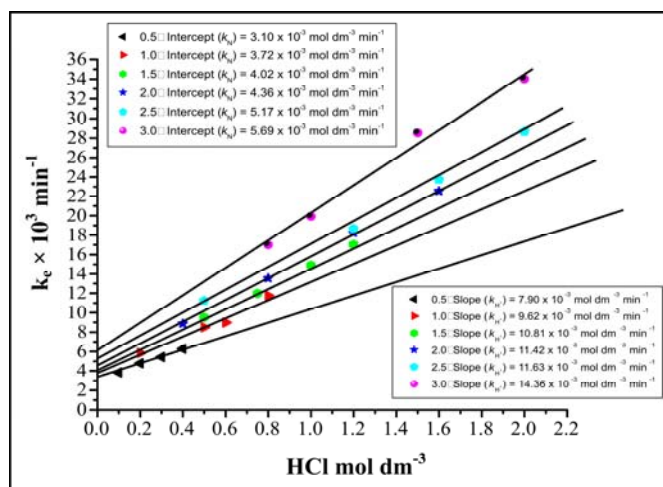
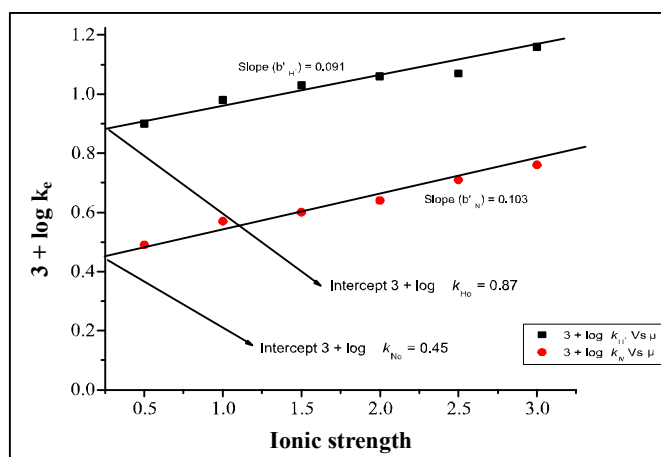


Fig. 2: Plot of $k_e \times 10^3$ versus $HCl \text{ mol dm}^{-3}$ for the hydrolysis of di-3-chloro-2-methyl aniline phosphate at constant ionic strength

The linearity of the plot with positive slope represents the acid catalyzed reaction and since the slope of the linear plot increases with increase in ionic strength, the hydrolysis via conjugate acid species exhibits positive salt effects. All the lines meet at different points on the rate axis, indicating the participation of neutral species. Different values of intercepts show that the contribution of neutral species at different acidities is varying. The accelerating ionic effect indicates that di-3-chloro-2-methylaniline phosphate undergoes hydrolysis with positive effect of ionic strength. The corresponding slope (specific acid catalyzed rate) and intercept values (neutral rate) at constant ionic strength are shown in Table 2. The specific acid catalyzed rates with their logarithmic value at that ionic strength are illustrated in Fig. 3.

Table 2: Specific acid catalyzed rates for the hydrolysis of di-3-chloro-2-methylaniline phosphate via conjugate acid and neutral species

Ionic strength (μ)	$k_{H^+} \times 10^3$ (min^{-1})	$3 + \log k_{H^+}$	$k_N \times 10^3$ (min^{-1})	$3 + \log k_N$
0.5	7.90	0.90	3.10	0.49
1.0	9.62	0.98	3.72	0.57
1.5	10.81	1.03	4.02	0.60
2.0	11.42	1.06	4.36	0.64
2.5	11.63	1.07	5.17	0.71
3.0	14.36	1.16	5.69	0.76

**Fig. 3: Log rate constant Vs ionic strength for acid catalysed hydrolysis of di-3-chloro-2-methyl aniline phosphate at constant ionic strength**

The slope of lines represents a constant b'_{H^+} , where $b' = b'/2.303$ and the intercepts on the log rate axis represent the specific acid-catalyzed rates ($\log k_{H^+}$). From the study of ionic strength effect, the total rates contributed by conjugate acid and neutral species may be calculated by the following second empirical term of Debye–Huckle equation¹⁴.

$$k_{H^+} = k_{H_0^+} \cdot \exp \cdot b'_{H^+} \cdot \mu \quad \dots(2)$$

Where, k_{H^+} , $k_{H_0^+}$, b'_{H^+} and μ are specific acid catalyzed rate at that ionic strength, specific acid catalyzed rate at zero ionic strength, a constant and ionic strength, respectively.

Specific acid catalyzed rate (k_H^+) can be converted into acid catalyzed rates ($k_H^+ \cdot C_{H^+}$) as follows:

$$k_H^+ \cdot C_{H^+} = k_{H_0^+} \cdot C_{H^+} \cdot \exp. b'_{H^+} \cdot \mu \quad \dots(3)$$

On taking logarithm

$$\log k_H^+ \cdot C_{H^+} = \log k_{H_0^+} + \log C_{H^+} + b'_{H^+} \cdot \mu \quad \dots(4)$$

Where, for HCl, C_{H^+} and μ are of the same value.

The neutral rate may be represented by following equation:

$$k_N = k_{N_0} \exp. b'_N \cdot \mu \quad \dots(5)$$

$$\log k_N = + b'_N \log k_{N_0} \cdot \mu \quad \dots(6)$$

Where k_N is neutral rate and $b'_N = b'_N / 2.303$. The overall hydrolysis was represented by following equation:

$$k_e = k_H^+ \cdot C_{H^+} + k_N \quad \dots(7)$$

Table 3 summarizes both the observed and theoretical rates of the hydrolysis in acid region 0.5 to 4.0 mol dm⁻³ HCl. The lowering in rate at 5.0, 6.0, and 7.0 mol dm⁻³ HCl may be attributed to the lowering in concentration of water molecule.

Table 3: Theoretical and experimental rate data for the hydrolysis of di-3-chloro-2-methylaniline phosphate

HCl (mol dm ⁻³)	$k_H^+ \cdot C_{H^+} \times 10^3$ (min ⁻¹)	$k_N \times 10^3$ (min ⁻¹)	$k_e \times 10^3$ (min ⁻¹)	- $\log(a_{H_2O})^n$	$k_e \times 10^3$ (min ⁻¹) Estd.	$k_e \times 10^3$ (min ⁻¹) Expt.
0.5	4.14	3.15	7.29		7.29	10.69
1.0	9.20	3.55	12.75		12.75	15.55
1.5	15.33	3.99	19.33		19.33	20.46
2.0	22.70	4.50	27.20		27.20	27.76
2.5	31.51	5.06	36.57		36.57	36.89
3.0	41.99	5.70	47.69		47.69	45.40

Cont...

HCl (mol dm ⁻³)	$k_{H^+} \cdot C_{H^+} \times 10^3$ (min ⁻¹)	$k_N \times 10^3$ (min ⁻¹)	$k_e \times 10^3$ (min ⁻¹)	- $\log(a_{H_2O})^n$	$k_e \times 10^3$ (min ⁻¹) Estd.	$k_e \times 10^3$ (min ⁻¹) Expt.
3.5	54.40	6.42	60.82		60.82	63.74
4.0	69.02	7.23	76.25		76.25	76.37
5.0	106.39	9.16	115.55	(0.16) ²	55.31	56.77
6.0	157.45	11.61	169.07	(0.21) ³	39.63	38.17
7.0	226.52	14.72	241.24	(1.28) ⁴	18.30	16.44

Equation (7) was used to calculate the theoretically estimated rates, which are then compared with the experimental rates. The rate beyond 4.0 mol dm⁻³ HCl was calculated employing the Bronsted-Bjerrum equation¹⁵:

$$k_e = k_{H^+} C_{H^+} (a_{H_2O})^n + k_N (a_{H_2O})^n \quad \dots(8)$$

$$k_{H^+} \cdot C_{H^+} = k_{H_0^+} \cdot C_{H^+} \cdot \exp.b'_{H^+} \cdot \mu (a_{H_2O})^n \quad \dots(9)$$

$$\log k_{H^+} \cdot C_{H^+} = \log k_{H_0^+} + \log C_{H^+} + b'_{H^+} \cdot \mu + n \log (a_{H_2O}) \quad \dots(10)$$

The neutral rate at higher concentration is as follow:

$$k_N = k_{N_0} \exp. b'_{N} \cdot \mu \cdot (a_{H_2O})^n \quad \dots(11)$$

$$\log k_N = \log k_{N_0} + b'_{N} \cdot \mu + n \log (a_{H_2O}) \quad \dots(12)$$

Where n is an integer and (a_{H2O}) is water activity. It is clear from the results that hydrolysis of di-3-chloro-2-methyl aniline phosphate in acid occurs via both conjugate acid species and neutral species, and their rates are subjected to positive ionic strength or water activity.

In the region from 0.5 to 4.0 mol dm⁻³ the rate law is calculated and shown in Equation (13).

$$k_e = 7.41 \times 10^{-3} \cdot C_{H^+} \exp.(0.091 \times 2.303) \cdot \mu + 2.81 \times 10^{-3} \cdot \exp. (0.103 \times 2.303) \cdot \mu \quad \dots(13)$$

The rate laws beyond 4.0 mol dm⁻³ HCl were calculated and shown in Equation (14)

$$k_e = 7.41 \times 10^{-3} \cdot C_{H^+} \exp. (0.091 \times 2.303) \cdot \mu \cdot (a_{H_2O})^n + 2.81 \times 10^{-3} \cdot \exp. (0.103 \times 2.303) \cdot \mu \cdot (a_{H_2O})^n \quad \dots(14)$$

Molecularity of the hydrolytic reaction

Molecularity of hydrolysis of di-3-chloro-2-methylaniline phosphate was determined by Zucker-Hammett hypothesis, Bunnett, and Bunnett Olsen parameter^{16,17}. The Zucker-Hammett hypothesis¹⁸ is made up of two parts. In the first part, Hammett postulated¹⁹ that the reactions that give a linear plot of log rate constants against the acidity function (-Ho) did not involve water molecules in the rate determining step. The slope value 0.59 (figure not shown) of the plot is far from unity, indicating the absence of unimolecular hydrolysis. The second part of the hypothesis deals with a plot between the log rate constant and log acid molarity. A unit or approximately unit slope of this plot was used as a criterion to predict the probable mechanism to be bimolecular. The slope value 1.17 (Fig. not shown) clearly indicates the bimolecularity of the reaction.

Bunnett suggested two parameters ω , ω^* . Former is the slope of plot between log rate constant + Ho and log activity of water ($-\log a_{\text{H}_2\text{O}}$). The slope value $\omega = 8.25$, $\omega^* = 3.04$, and $\phi = 1.51$ for Bunnett and Bunnett-Olsen parameters^{15,16} (figure not shown) for di-3-chloro-2-methyl aniline phosphate ester also indicate a slow proton transfer with a nucleophilic attack of the water molecule.

Effect of temperature

Arrhenius parameters²⁰ determined for the hydrolysis at 4.0 mol dm⁻³ HCl, which are shown in Table 4. The magnitude of the Arrhenius parameters falls in the range of bimolecular reaction.

Table 4: Arrhenius parameters for acid catalyzed hydrolysis of di-3-chloro-2-methylaniline phosphate

HCl (mol dm ⁻³)	Slope	E _a (kcal/mol)	A (sec ⁻¹)	-ΔS [‡] (e.u.)
4	-0.030	13.73	2.39 × 10 ⁷	27.12

Effect of solvent

The effect of solvent on rate of hydrolytic reaction indicates the transition state in which charge is dispersed. This is accordance with Chanley's observation²¹. Table 5 shows that the rate constant value gradually increases with the gradual addition of 1,4 dioxane and DMSO. Dioxane is regarded as polar aprotic solvent while dimethylsulfoxide is regarded as dipolar aprotic solvent.

Table 5: Solvent effect rate data for acid catalyzed hydrolysis of di-3-chloro-2-methylaniline phosphate

HCl (Mol dm ⁻³)	% Solvent v/v	1,4-dioxane	DMSO
		$k_e \times 10^3$ (min ⁻¹)	$k_e \times 10^3$ (min ⁻¹)
4.0	20	43.78	60.54
4.0	30	60.95	79.43
4.0	40	76.37	82.25
4.0	50	88.54	92.68

Bond-cleavage of reaction

Bimolecular nature of hydrolysis of di-3chloro-2-methylaniline phosphate involving P-N bond fission is further supported by comparative kinetic rate data and isokinetic relationship plot. Comparative kinetic rate data for hydrolysis of other diesters studied kinetically is summarized in Table (6). The isokinetic relationship plot ($-\Delta S^\ddagger$ vs E_a) shows point of di-3-chloro-2-methylaniline phosphate is collinear with other diesters, which are known to undergo bimolecular hydrolysis via P-N bond fission (Fig not Shown).

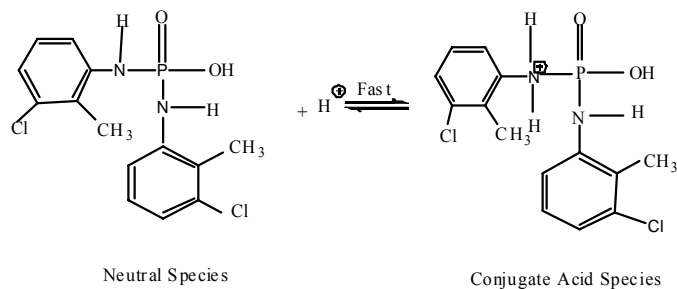
Table 6: Comparative kinetic rate data for hydrolysis of some diesters via conjugate acid species

Diesters	HCl mol dm ⁻³	E_a (kcal/mol)	$-\Delta S^\ddagger$ (e.u.)	Molecularity	Bond fission
Cyclohexyl amine phosphate	3	12.09	37.11	2	P-N
<i>O</i> -Toluidine	1	11.40	38.66	2	P-N
Phenatadine phosphate	3	5.72	70.55	2	P-N
<i>m</i> -Toluidine	3	15.56	21.29	2	P-N
2-Chloroaniline	3	13.70	28.90	2	P-N
2-Methyl-5-nitroaniline	4	12.81	29.78	2	P-N
3-Chloro-2-methylaniline	4	13.72	27.12	2	Present work

Mechanism

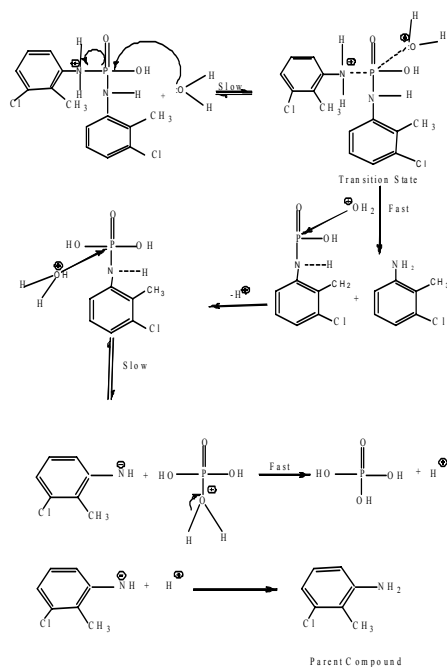
The mechanism of hydrolysis of di-3-chloro-2-methylaniline phosphate via conjugate acid species is shown **Scheme 1** and **2**.

(a) Formation of conjugate acid species by fast pre-equilibrium proton transfer:



Scheme 1

(b) Bimolecular nucleophilic attack of water on phosphorus via conjugate acid species $S_N^2(P)$



Scheme 2

CONCLUSION

Di-3-chloro-2-methyl aniline phosphate ester in 0.5-7.0 mol dm⁻³ HCl was found to hydrolyze via neutral and conjugate acid species. The acid catalysed hydrolysis is subjected to the positive effect of the ionic strength. The bimolecular nature of hydrolysis was supported by different parameters such as Hammett, Zucker-Hammett, Bunnett and Bunnett-Olsen parameters. Bimolecular hydrolysis with P-N bond fission of di-3-chloro-2-methylaniline phosphate was proposed S_N² (P) mechanism has been suggested for the hydrolysis via conjugate acid species.

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