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Synthesis, Mechanistic Interpretation And Kinetic Study Of Potentially Active Substituent Of 2, 4, 6, Trimethylaniline Phosphate Di-Ester.

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ABSTRACT

Organic phosphate have found a broad range of application in the area of industrial, agriculture and medicinal chemistry owning to their biological and physical properties, as well as their utility as synthetic intermediates. The Kinetic study of derivatives of phosphoric acid was not much exploited but since the phosphate esters have important role in various branches of chemistry particularly biochemistry[5]. Kinetic studies of these esters prove that, there are some common reaction paths, which are followed both chemically and biochemically. Macromolecules such as deoxyribonucleic acid (D.N.A.) and ribonucleic acid (R.N.A.) that involve common (C-O-P)[6-21] and (C-N-P)[22-40] linkages. Organic phosphorus compounds are enjoying relatively rapid growth and great deal of research efforts due to their industrial applications in various fields. There is a growing interest of investigators in the mechanism of biochemical processes. Kinetic study of hydrolysis of di-2,4,6-trimethylaniline phosphate has been accomplished in 20% aqueous dioxan mixture at 95±0.5°C in 0.1 to 6.0 mol.dm.$^{-3}$HCl, and pH 1.24 to 7.46. The pH-log rate profile shows the maxima at 4.0 mol. dm.$^{-3}$HCl. After that rate of hydrolysis decreases with increase in acid molarity and from pH 1.24 to 4.17, the rates were increased. Further increase in pH from 4.17 to 7.46, the rates are decreased. Results shows that di-ester is reactive in the form of conjugate acid, neutral and mono-negative species. Effect of pH, solvent, temperature and concentration etc. on the rate of hydrolysis have been studied to determine the reaction paths. Ionic strength data and pK values have been used to determine the reactive species and to compare the estimated rates with those of experimental rates. The rates were found to be enclosed agreement with the experimental rates. Molecularity of reaction were discussed in terms of recent concepts such as Hammett acidity function [1],Zucker-Hammett Hypothesis[2] and Bunnett parameters[3] etc. Fission has been suggested on the basis of comparative Kinetic rate data and isokinetic relation[4]. It has been observed that the hydrolysis of di-ester takes place through its conjugate acid, neutral, di-negative species in different ranges of acid and buffer medium. Conjugate acid, neutral and di-negative species have been found to be more reactive than acid species.

Keywords: Synthesis, Mechanism, Substituent effect ,2,4,6-trimethylaniline phosphate, di-ester, acid medium.

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INTRODUCTION

Organic phosphate have found a broad range of application in the area of industrial, agriculture and medicinal chemistry owning to their biological and physical properties, as well as their utility as synthetic intermediates. The Kinetic study of derivatives of phosphoric acid was not much exploited but since the phosphate esters have important role in various branches of chemistry particularly biochemistry [5]. Kinetic studies of these esters prove that, there are some common reaction paths, which are followed both chemically and biochemically. Macromolecules such as deoxyribonucleic acid (D.N.A.) and ribonucleic acid (R.N.A.) that involve common (C-O-P)[6-21] and (C-N-P)[22-40] linkages.

Organic phosphorus compounds are enjoying relatively rapid growth and great deal of research efforts due to their industrial applications in various fields. There is a growing interest of investigators in the mechanism of biochemical processes.

EXPERIMENTAL

2,4,6, trimethylaniline phosphate di-ester was synthesized by the Rudert method,[41].

The method of preparation of the residue left after removing 2,4,6, trimethylaniline phosphate monoester at b_{70} 80-90°C was washed several times with boiling distilled water and add 0.1 N NaOH solution is added to remove 2,4,6, trimethylaniline phosphate monoester, unreacted $POCl_3$ and the amine, finally digested in 5.0 N NaOH solution (to separate di-ester of 2,4,6, trimethylaniline phosphate) filtrate was acidified with dilute HCl using phenolphthalein as an indicator. A white precipitate is obtained was separated by filtration and made free hydroxylions with repeated washings with boiling water. It was then dried at room temperature and recrystallized with absolute ethyl alcohol to give white crystalline solid which was identified to be di-2,4,6, trimethylaniline phosphate.

Finally the structure was confirmed by Infrared spectrum (IR)

RESULT AND DISCUSSION

Hydrolysis of 2,4,6, trimethylaniline phosphate Di-ester has been kinetically studied in 0.1 to 6.0 mol. dm^{-3}HCl at 97±0.5 °C. Table-1 summarizes the first order coefficient and Table-1 describes the pH - log rate profile.

Table I: pH-log RATE PROFILE OF DI-2,4,6-TRI- METHYLANILINE PHOSPHATE AT 97±0.5 °C

HCl mol.dm.$^{-3}$	pH	$10^5.K_e$ (mol.dm.$^{-3}$ min.$^{-1}$) (Obsd.)	5+log K_e
6.0	-0.778	46.22	1.66
5.0	-0.699	90.24	1.96
4.0	-0.602	149.95	2.18
3.5	-0.544	141.06	2.15
3.0	-0.477	136.34	2.13
2.5	-0.397	119.73	2.08
2.0	-0.300	111.70	2.05
1.5	-0.176	91.52	1.96
1.0	0.000	83.53	1.92
0.5	0.301	62.84	1.80
0.4	0.400	61.48	1.79
0.3	0.520	57.61	1.76

0.2	0.700	52.92	1.72
0.1	1.000	49.28	1.69
Buffers-	1.24	38.53	1.59
composition	2.20	35.34	1.55
of buffers	3.33	32.81	1.52
have been	4.17	27.55	1.44
given in	5.60	12.68	1.10
experimental	6.43	9.14	0.96
section	7.46	8.49	0.93

Table-2: HYDROLYSIS OF DI-2,4,6-TRIMETHYLANILINE PHOSPHATE AT CONSTANT IONOC STRENGTH AT 97±0.5 °C.

Ionic Strength (μ) (mol.dm-3)	COMPOSITION		$10^5.K_e$ $(mol.dm.^{-3}\ min.^{-1})$ (Obsd.)
	HCl (mol.dm-3)	KCl (mol.dm-3)	
1.0	0.2	0.8	49.70
1.0	0.4	0.6	57.91
1.0	0.6	0.4	63.44
1.0	0.8	0.2	71.03
1.0	1.0	0.0	83.53
2.0	0.2	1.8	44.36
2.0	0.5	1.5	52.72
2.0	1.0	1.0	69.91
2.0	1.5	0.5	83.62
2.0	1.8	0.2	95.52
2.0	2.0	0.0	111.70
3.0	0.5	2.5	47.30
3.0	1.0	2.0	61.24
3.0	1.5	1.5	74.00
3.0	2.0	1.0	86.82
3.0	2.5	0.5	102.74
3.0	3.0	0.0	136.37

It is clear the rate of hydrolysis increases with increase in acid molarity upto 4.0 mol dm^{-3}HCl and further rise in acidity decreases the rate of hydrolysis (>4.0 mol.dm^{-3}HCl) the cause of the bend in pH – log rate profile is due to either.

The rate maxima or bend of pH log - rate profile in acid medium have also been found in some other cases.

In Organic phosphate calorimetrically [42] similar rate maxima were observed due to full conversion of neutral species into their conjugate acid species, the rate should remain constant but it further increases in increase acid molarity, decreases the rate of hydrolysis. The cause of the bend may not be due to maximum protonation.

EFFECT OF IONIC STRENGTH

The effect of Ionic strength was examined by carrying out kinetic runs at constant ionic strength which were obtained by appropriate mixtures of KCl and HCl at 97±0.5°C. The rate coefficient have been summarized in Table-2 and TABLE-II describes a plot between rate constant and acid molarities.

(TABLE-II) shows that three linear curves were obtained which intersect on the rate axis represents the corresponding specific neutral rates at the ionic strength, thus both the specific neutral rates and specific acid catalyst rates are subjected to the negative effect of ionic strength.

Table-3: SPECIFIC ACID CATALYSED AND SPECIFIC NEUTRAL RATES FOR THE HYDROLYSIS OF DI-2,4,6-TRIMETHYLANILINE PHOSPHATE AT DIFFERENT IONIC STRENGTH AT 97±0.5 °C.

Ionic strength (μ)	$10^5.K_{H+}$ (mol.dm.$^{-3}$ min.$^{-1}$)	5+lok K_{H+}	$10^5.K_N$ (mol.dm.$^{-3}$ min.$^{-1}$)	5+log K_N
1.0	35.71	1.55	42.00	1.62
2.0	31.81	1.50	38.00	1.58
3.0	26.78	1.43	33.00	1.52

Table-4: SPECIFIC ACID CATALYSED [K_{H0+}] AND SPECIFIC NEUTRAL [K_{N0}] RATES FOR THE HYDROLYSIS OF DI-2,4,6-TRIMETHYLANILINE PHOSPHATE AT ZERO IONIC STRENGTH AT 97±0.5 °C.

$10^5.K_{H0+}$ (mol.dm.$^{-3}$ min.$^{-1}$)	5+log K_{H0+}	b_{H+}	$10^5.K_{N0}$ (mol.dm.$^{-3}$ min.$^{-1}$)	5+log K_{N0}	b_N
37.15	1.57	0.0181	43.65	1.64	-0.0207

(TABLE-III) and (Table- IV) describes the relation between log rate coefficient and ionic strength and Table -3 summarizes the log rate coefficient at that ionic strength.

(TABLE- III and IV) show that Linear curves are obtained, the slope of these curves represent the b_{H+} and b_N where (b'=b/2.303) The rate axis specific acid catalyzed (log K_{HO+}) and specific neutral rates (logK_{N0}) at zero ionic strength respectively (Table-4) summarizes the rate coefficients of specific acid catalyzed and specific neutral rate at zero ionic strength with their corresponding :

TABLE-II show that three linear curves represent the rate of hydrolysis of that ionic strength by the following rate equation.

$$K_e = K_{H+}.\ C_{H+} + K_N \quad \text{--- (1)}$$

Where K_e, K_{H+} and K_N are the observed rate constant, specific acid catalyzed rate and neutral rate respectively at that ionic strength and C_{H+} is the hydrogen ion concentration.

2. All the three lines started from different points indicate the presence of neutral hydrolysis in strong acid region.

Similar results have been observed in the case of di-3,4 di- chloroaniline phosphate,[36] and di-p-propoxy-aniline phosphate,[31]. The intercepts on the rate of axis represent the corresponding specific neutral rate at the ionic strength , which decreases with increase in ionic strength. Therefore , the rate of hydrolysis via neutral species is also subjected to ionic retardation effect.

Table III & IV describe a relation between log rate coefficient and ionic strength linear curves are obtained, the slope of these curves represent the constant b_{H+} and $b_{N'}$ while the intercept on the log rate axis represents the specific acid catalyzed rate and specific neutral rate at zero ionic strength which can be used following equation to calculate the acid catalyzed rate or neutral rates.

Acid rates can be shown as:

$K_{H+} = K_{H0+}\ .\exp.\ b_{H+}\ .\ \mu$ ---eq (2)

$K_{H+} = 37.15\times10^{-5}\ \exp.\ (-0.0181).\mu$

Or,

$K_{H+}.C_{H+} = 37.15\times10^{-5}\ .\ C_{H+}\ .\exp.\ (-0.0181).\mu$

Or,

$5+\log K_{H+}.\ C_{H+} = 1.57 + \log C_{H+} + (-0.0181).\mu$ ---eq(3)

NEUTRAL RATES:

$K_N = K_{N0+}\ .\exp.\ (-0.0207).\mu$

or, $K_N = 43.65\times10^{-5}.\ \exp.\ (-0.0207).\mu$

or, $5+\log K_N = 1.64 + (-0.0207).\mu$ --eq(4)

The neutral rates may be denoted as -

$K_{H+}.C_{H+}$ and K_N are acid catalysed and neutral rates, ($5+\log K_{H0+}$) and ($5+\log K_{N0}$) are the log form of specific acid catalysed and specific neutral rates at zero ionic strength respectively.

The equation 3 and 4 only be used to compute the acid catalyzed rates and neutral rates at each experimental acid molarity. Thus acid catalyzed and neutral rates may be represented the total rate of acid medium as increase in ionic strength.

It is an ionic retarding effect which indicate that di- 2,4,6-trimethylaniline Phosphate undergoes acid catalyzed hydrolysis with negative effect of ionic strength.

$5+\log K_{H+}.\ C_{H+} = 5+\log K_{H0+} + \log C_{H+} + b'_{H+}\ .\ \mu + n\log(a_{H2O})$ -eq(5)

and neutral rates can be represented as

$5+\log K_N = 5+\log K_{N0} + b'_{N+}\ .\ \mu + n\log(a_{H2O})$ - eq(6)

Where(a_{H2O}) is the water activity parameter and n is an integer

Where, n=0 for 1.0 to 4.0 mol.dm^{-3}HCl and n*=2,3 respectively for 5.0 and 6.0 mol.dm^{-3}HCl for acid rates and neutral rates.

Table-5 summarizes both the observed and calculated rates of hydrolysis for the acid region from 1.0 to 6.0 mol.dm^{-3}HCl.

Table-5: CALCULATED AND OBSERVED RATES FOR THE HYDROLYSIS OF DI-2,4,6-TRIMETHYLANILINE PHOSPHATE AT 97±0.5°C.

HCl (mol.dm.$^{-3}$)	pH	$10^5.K_N$ (mol.dm.$^{-3}$ min.$^{-1}$)	5+log K_N	$10^5.K_{H+}. C_{H+}$ (mol.dm.$^{-3}$ min.$^{-1}$)	$10^5.K_{H+}. C_{H+}$ (mol.dm.$^{-3}$ min.$^{-1}$)	$10^5.K_N$ (mol.dm.$^{-3}$ min.$^{-1}$)	$10^5.K_e$ (mol.dm.$^{-3}$ min.$^{-1}$) (Calcd.)	5+log K_e (Calcd.)	$10^5.K_e$ (mol.dm.$^{-3}$ min.$^{-1}$) (Obsd.)
0.1	1.000	43.44	1.64	3.70			47.14	1.67	49.28
0.2	0.700	43.23	1.63	7.35			50.58	1.70	52.92
0.5	0.301	42.62	1.63	18.19			60.81	1.78	62.84
1.0	0.000	41.62	1.62	35.64			77.26	1.89	83.53
1.5	-0.176	40.64	1.61	52.34			92.98	1.97	91.52
2.0	-0.300	39.68	1.60	68.20			107.88	2.03	111.7
2.5	-0.397	38.75	1.59	83.51			122.26	2.09	119.73
3.0	-0.477	37.83	1.58	98.33			136.16	2.13	136.34
3.5	-0.544	36.94	1.57	112.37			149.31	2.17	141.06
4.0	-0.602	36.07	1.56	128.42			164.49	2.21	149.95
5.0	-0.699	34.39	1.54	150.90	73.87	16.85	90.72	1.96	90.24
6.0	-0.778	32.79	1.52	34.60	40.40	7.63	48.03	1.68	46.22

n=0 for 0.1 to 4.0 mol.dm.-3 HCl and n*=2,3 respectively for 5.0 and 6.0 mol.dm.-3 HCl.

It is clear from the results that there is fairly good agreement between experimentally observed rates upto 4.0 mol.dm^{-3}HCl but beyond 4.0 mol.dm^{-3}HCl there is steep fall in the rate which has been presumed due to participation of water molecule as a second reaction partner in the nucleophilic substitution reaction.

CONCEPT OF MOLECULARITY

The molecularity of solvolytic reaction of acid catalysed hydrolysis of di-2,4,6-tri-methylaniline phosphate was determined by Zucker-Hammett plot,[2]Bunnett plot,[3] , Bunnettolsen plot, [43].

The Zucker in collaboration with Hammett put forwarded a hypothesis. First part of which involve a correlation between log-rate constant and Hammett acidity function[1][-H_0]. This plot (Tableure not shown) shows a straight line with slop value (0.24), which is far from unity, shows that the rate of hydrolysis of di-2,4,6-tri-methylaniline phosphate via conjugate acid species followed by bimolecular hydrolytic reaction.

The second part of hypothesis deals with a plot between the log-rate constant and log acid molarity. A unit of approximately unit slope of the plot was used as a criterion to predict the probable mechanism to be biomolecular. The slope value 0.617(Tableure 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 +$H_0$and log activity of water (-log a_{H2O}). The slope value ω = 10.71, ω*=4.17 and ϕ=1.52 for Bunnett and Bunnett-olsen plot[43] (Tableure not shown) for di-2,4,6-tri-methylaniline phosphate ester also indicates a slow proton transfer with a nucleophilic attack of the water molecules.

EFFECT OF TEMPERATURE

Arrhenius parameter [44-46] determined for the hydrolysis at 3.0 mol.dm^{-3}HCl,

ΔE = 18.76 K.cal mol^{-1} frequency factor A=2.739x10^{6}sec^{-1} ΔS$^{\#}$=31.50 e.u and at 5.0 mol dm^{-3}HCl ΔE=19.21 K.cal mol^{-1}frequency factor A=3.140x10^{6}sec^{-1} ΔS$^{\#}$=31.23

EFFECT OF SOLVENT

The effect of solvent on the rate of hydrolysis at 3.0 and 5.0 mol.dm^{-3}. HCl has been studied by carrying out kinetic runs for different mixtures of aqueous-dioxan at 97±0.5°C. Hydrolysis of the conjugate acid species both uni- or bimolecularly, would involve dispersion of positive charge in transition state, such a reaction would be favored less, by the less polar solvent medium and the changes in rates by a change over from more to less polar solvent should not be very insignificant. The effect of solvent for the rate of hydrolysis of di-2,4,6-tri-methylaniline phosphate have been summarized in Table-12. There is a slight decrease in rates by a change over from less to more polar dioxan content.

Table- 6: HAMMETT PLOT DATA FOR THE RATE OF HYDROLYSIS OF DI-2,4,6-TRI-METHYLANILINE PHOSPHATE AT 97±0.5 °C.

HCl (mol.dm.$^{-3)}$	10^5.K_e (mol.dm.$^{-3}$ min.$^{-1}$) (Obsd.)	5+log K_e	-H_0	-log(a_{H2o})
1.0	0.20	83.53	1.92	0.017
1.5	0.47	91.52	1.96	0.027
2.0	0.69	111.70	2.05	0.039
2.5	0.87	119.73	2.08	0.053
3.0	1.05	136.34	2.13	0.070
3.5	1.23	141.06	2.15	0.087
4.0	1.40	149.95	2.18	0.105
5.0	1.76	90.24	1.96	0.155
6.0	2.12	46.22	1.66	0.211

Table- 7: ZUKER-HAMMETT PLOT DATA FOR THE RATE OF HYDROLYSIS OF DI-2,4,6-TRI-METHYLANILINE PHOSPHATE AT 97±0.5 °C.

HCl (mol.dm.$^{-3)}$	log C_{H+}	10^5.K_e (mol.dm.$^{-3}$ min.$^{-1}$) (Obsd.)	5+log K_e
1.0	0.000	83.53	1.92
1.5	0.176	91.52	1.96
2.0	0.300	111.70	2.05
2.5	0.397	119.73	2.08
3.0	0.477	136.34	2.13
3.5	0.544	141.06	2.15
4.0	0.602	149.95	2.18
5.0	0.699	90.24	1.96
6.0	0.778	46.22	1.66

Table-8: OLD BUNNETT AND BUNNETT-OLSEN PLOT DATA FOR THE RATE OF HYDROLYSIS OF DI-2,4,6-TRI-METHYLANILINE PHOSPHATE AT 97±0.5 °C.

HCl (mol.dm.$^{-3)}$	log C_{H+} (a)	10^5.K_e (mol.dm.$^{-3}$ min.$^{-1}$) (Obsd.)	5+log K_e (b)	-H_0	5+log K_e– logC_{H+} (b-a)	(5+log K_e+ H_0) (b-c)	-(-logC_{H+} +H_0)	-log (a_{H2O})
1.0	0.000	83.53	1.92	0.20	1.92	1.71	0.20	0.017
1.5	0.176	91.52	1.96	0.47	1.784	1.49	0.294	0.027
2.0	0.300	111.70	2.05	0.69	1.75	1.36	0.39	0.039
2.5	0.397	119.73	2.08	10.87	1.683	1.21	0.473	0.053
3.0	0.477	136.34	2.13	1.05	1.653	1.08	0.573	0.070
3.5	0.544	141.06	2.15	1.23	1.606	0.92	0.686	0.087

4.0	0.602	149.95	2.18	1.40	1.578	0.78	0.798	0.107
5.0	0.699	90.24	1.96	1.76	1.261	0.2	1.061	0.155
6.0	0.778	46.22	1.66	2.12	0.882	-0.46	1.342	0.211

Table- 9: EFFECT OF SOLVENT ON THE RATE OF HYDROLYSIS OF DI-2,4,6-TRI-METHYLANILINE PHOSPHATE AT 97±0.5°C.

HCl (mol.dm.$^{-3)}$	Water Percentage (v/v)	Dioxan Percentage (v/v)	$10^5.K_e$ (mol.dm.$^{-3}$ min.$^{-1}$) (Obsd.)
3.0	100.00	0.00	136.34
3.0	60.00	40.00	110.94
3.0	50.00	50.00	85.42
5.0	80.00	20.00	90.24
5.0	60.00	40.00	75.91
5.0	50.00	50.00	61.19

Table-10: COMPARATIVE ISOKINETIC RATE DATA FOR THE HYDROLYSIS OF SOME PHOSPHATE DI-ESTERS VIA THEIR CONJUGATE ACID SPECIES.

S. No.	Phosphate di-ester	Temp. °C	Medium	E. K. cal/ mol	$-\Delta S^{-}$ (e.u.)	Bond fission	Reference
1	o-toludine	50	1.0	11.49	38.66	P-N	213
2	4-chloro-3, methylaniline	97	3.0	27.35	7.41	P-N	224
3	5-chloro, 2-methylaniline	80	3.0	21.5	20.80	P-N	94
4	m-toludine	80	4.0	14.62	32.94	P-N	3
5	m-nitoaniline	98	3.0	16.61	31.90	P-N	219
6	cyclohexylamine	50	5.0	12.09	37.11	P-N	161
7	p-nitroaniline	98	2.0	14.64	46.46	P-N	3
8	p-chloroaniline	90	4.0	9.15	56.78	P-N	16
9	p-phentidine	98	3.0	5.72	70.55	P-N	85
10	α-naphthylamine	98	3.0	23.57	12.71	P-N	3
11	2,4,6,-tri-methylaniline	97	3.0	18.76	31.50	P-N*	This
		97	5.0	19.21	31.23	P-N*w	ork

BOND-CLEAVAGE OF REACTION

The hydrolysis of di-2,4,6-tri-methylaniline phosphate may involve P-N or C-N bond fission in the transition state, formed due to bimolecular nucleophilic attack of water molecule, it is seen from the discussion that the Zucker-Hammett hypothesis[2], Bunett parameters[3] Arrhenius parameters [44-46] and other relevant evidences favor bimolecular nature of hydrolysis of 2,4,6-tri-methylaniline phosphate di-ester and radioactive tracer technique method may be used (H_2O^{18}) to decide the rapture of bond fission as the reaction medium, and analyzing the product formed, but due to lack of experimental facilities this method could not persuaded.

Other reliable and suitable method of isokinetic relationship has been used. The corresponding comparative isokinetic rate data have been summarized in Table-13 describes the isokinetic relationship plot($-\Delta S^{\#}$vs E) of other similarly substituted aryl amino phosphate di-ester, which invariably undergo bimolecular hydrolysis via P-N bond fission. Consequently, the conjugate acid species of 2,4,6-tri-methylaniline phosphate di-ester undergoes bimolecular hydrolysis with P-N bond fission.

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