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Kinetic and Mechanistic Studies of Hydrolysis of 2-Ethyl-6-methylaniline Phosphate Tri-Ester in Acidic Medium

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Kinetic investigation of the hydrolysis of 2-ethyl-6-methylaniline phosphate tri-ester has been carried out in 0.1 to 6.0 mol dm^{-3} HCl and pH 1.24 to 7.46 at 97 ± 0.5 ºC in 30 % (v/v) aqueous dioxane mixture. Concentration of tri-ester in all kinetic runs was 5.0×10^{-4} mol dm^{-3}. The rate of hydrolysis was determined by measuring the rate of appearance of inorganic phosphate by Allen's modified colorimetric method. Pseudo first order rate coefficient have been calculated. Conjugate acid, neutral and mononegative species have been found to be reactive and contribute in over all rate. The rate coefficients estimated fairly in good agreement with the observed rates. Bond fission, molecularity and order of reaction have been suported by Arrhenius parameters, Zucker-Hammett hypothesis, concentration, solvent effect, *etc*. Comparative isokinetic rate data of similarly substituted other amino phosphate tri-ester, supported P–N bond fission.

Key Words: Kinetics, 2-Ethyl-6-methylaniline Phosphate tri-ester, Acidic medium.

INTRODUCTION

The effect of substituents on the rate of hydrolysis of aryl phosphate tri-esters having C–N–P linkages have been studied exhaustatively[1-8] and established that substituents of graded polarity[9,10] not only effect the reaction rate, but also the course of their reaction paths. It showed that the order of electron attracting power of the substituents in the aryl part. The rate of hydrolysis of 2-ethyl-6-methylaniline phosphate tri-ester was shown to be the least in the series of other tri-esters studied. A systematic ionic strength data shows the presence of acid catalysis and the order of rate values correlated well with the leaving abilities of organic substituents with P–N bond fission[11].

EXPERIMENTAL

2-Ethyl-6-methylaniline phosphate tri-ester has been prepared by the general methods[12]. The parent compound 13.5 mL was dissolved in 200 mL of dry benzene in round bottom flask and 10 mL of $POCl_3$ was added drop by drop with constant stirring to the ice cooled amine with the help of separating funnel for about 0.5 h. After the addition of $POCl_3$, it was refluxed for 50 h on Soxhlet heater at constant temperature in order to ensure complete reaction and distilled at reduced pressure. The first fraction of benzene and unreacted $POCl_3$ was removed by distillation at 50-55 ºC. The second fraction was dichloridate, it was dissolved in 100 mL of ice cooled water and kept at low temperature overnight and extracted with solvent ether. After removing the solvent ether, a light brown coloured crystalline solid was obtained, which on recrystallization with absolute ethyl alcohol gave a white crystalline solid, it was identified to be phosphate mono-ester.

The residue left after removing phosphate mono-ester washed several times with distilled water and add 0.1 N NaOH solution to remove mono-ester, unreacted $POCl_3$ and the parent amine, finally digested in 0.5 N NaOH solution (to separate di-ester from tri-esters) and filtrate was acidified with dilute HCl using phenopthalein indicator. A white precipitate so obtained was separated by filtration and washed many times with boiling distilled water to render it free from hydroxyl ions. It was then dried off and recrystallized with absolute ethyl alcohol to give a white crystalline solid which was identified to be tri-2-ethyl-6-methylaniline phosphate tri-ester by the following characteristics: m.p. 310 ºC, theoretical (observed) (%) $\rho = 7.01$ (7.54). IR (KBr, ν_{max}, cm^{-1}): 3395-3320 (N-H), 2910-2650 (C–H), 1710-1615 (aromatic ester), 1590-1520 (–C=C–), 1265-1180 (–P=O), 700-610 (substituted aromatic ring).

RESULTS AND DISCUSSION

The kinetic investigation of the hydrolysis of 2-ethyl-6-methylaniline phosphate tri-ester has been carried out in 0.1 to 6.0 mol dm^{-3} HCl and pH 1.24 to 7.46 at 97 ± 0.5 ºC in 30 % (v/v) aqueous dioxane mixture. The rate of hydrolysis was determined by measuring the rate of appearance of inorganic phosphate by Allen's modified colorimetric method[13]. Detailed kinetic study has been made at constant ionic strength to estimate theoritical acid-catalyzed rates. Effect of variables, such as temperature, solvent, ionic strength and substrate concentration, *etc.* on the rate of hydrolysis of ester have been studied in detail.

Hydrolysis *via* conjugate acid species: Hydrolysis of tri-phosphate ester has been investigated in the acid region from 0.1 to 6.0 mol dm^{-3} HCl and pH 1.24 to 7.46 in 30 % (v/v) aqueous dioxane mixture. Pseudo first order rate coefficients have been summarized in Table-1. As seen that the rate of hydrolysis of the tri-ester rises with the increase in acidity, the rate of hydrolysis decreases with the rate maxima at 4.0 mol dm^{-3} HCl. The initial rise in rate may be due to incursion of more reactive conjugate acid species.

TABLE-1
pH-log RATE PROFILE OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT 97 ± 0.5 ºC

HCl (mol dm^{-3})	pH	$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (obs.)	5 + log K_e
6.0	-0.778	34.57	1.54
5.0	-0.699	67.05	1.83
4.0	-0.602	130.68	2.12
3.5	-0.544	120.57	2.08
3.0	-0.477	110.03	2.04
2.5	-0.397	102.31	2.01
2.0	-0.300	89.71	1.95
1.5	-0.176	79.14	1.90
1.0	-0.000	65.30	1.81
0.5	0.301	50.01	1.70
0.4	0.400	45.74	1.66
0.3	0.520	41.87	1.62
0.2	0.700	38.52	1.59
0.1	1.000	36.16	1.56
Buffers: Composition of buffers have been given in experimental section	1.24	32.43	1.51
	2.20	24.11	1.38
	3.33	17.70	1.25
	4.17	12.77	1.11
	5.60	11.27	1.05
	6.43	10.25	1.01
	7.46	8.97	0.95

Effect of ionic strength: In order to examine the effect of ionic strength on the rate of hydrolysis of tri-ester, systematic kinetic runs at constant ionic strength using appropriate mixtures of KCl and HCl at three different ionic strength (1, 2 and 3 µ) were used to determined the rate of coefficients, which have been summarized in Table-2.

As clear from the plot (Fig. 1) three linear curves were obtained on the hydrolysis of tri-ester, each curve represents the hydrolysis at different ionic strength. The kinetic law for each curve may be represented as:

$$K_e = K_{H^+} \,.\, C_{H^+} \qquad (1)$$

where, K_e, K_{H^+} and C_{H^+}, respectively are observed rate constant, specific rate constant and acid molarities at that ionic strength, the acid catalyzed rate are subjected to negative effect of ionic strength. Hence, specific acid catalyzed rate (K_{H^+}) decreases with the increasing the ionic strength. Table-3 summarizes log rate coefficients at respective ionic strength.

Two linear curves are obtained from the (Fig. 2) the slopes of these curves represent the constant b'_{H^+} and b'_N (where b′ = b/2.303), while the

TABLE-2
HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT DIFFERENT IONIC STRENGTH AT 97 ± 0.5 ºC

Ionic strength (μ) (mol dm^{-3})	Composition		$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (obs.)
	HCl (mol dm^{-3})	KCl (mol dm^{-3})	
1.0	0.2	0.8	33.21
1.0	0.4	0.6	38.77
1.0	0.6	0.4	44.37
1.0	0.8	0.2	50.63
1.0	1.0	0.0	65.30
2.0	0.2	1.8	29.07
2.0	0.5	1.5	35.95
2.0	1.0	1.0	48.21
2.0	1.5	0.5	59.26
2.0	1.8	0.2	67.29
2.0	2.0	0.0	89.71
3.0	0.5	2.5	29.41
3.0	1.0	2.0	40.55
3.0	1.5	1.5	48.72
3.0	2.0	1.0	58.27
3.0	2.5	0.5	67.89
3.0	3.0	0.0	110.03

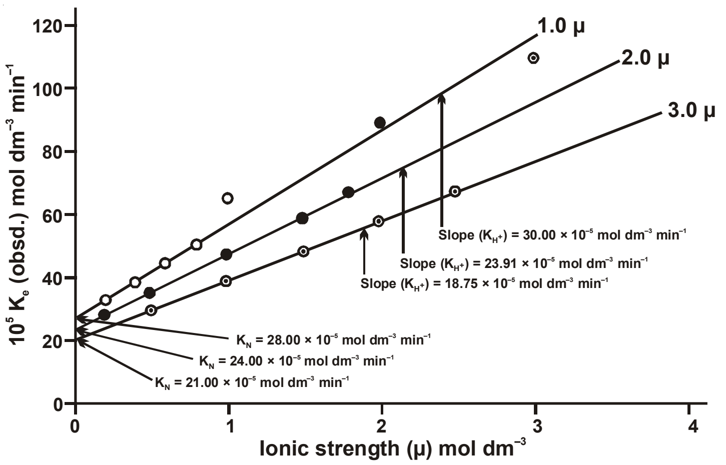


Fig. 1. Hydrolysis of tri-2-ethyl-6-methylaniline phosphate at different ionic strength at 97 ± 0.5 ºC

intercept on the log rate axis represents the specific acid catalyzed rate (log $K_{H_0^+}$) and specific neutral rate $(\log K_{N_0})$ at zero ionic strength, which have been summarized in Table-4.

TABLE-3
SPECIFIC ACID CATALYZED AND SPECIFIC NEUTRAL RATES FOR THE HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT DIFFERENT IONIC STRENGTH AT 97 ± 0.5 ºC

Ionic strength (µ)	$10^5 \cdot K_{H^+}$ (mol dm^{-3} min^{-1})	5 + log K_{H^+}	$10^5 \cdot K_{H_N}$ (mol dm^{-3} min^{-1})	5 + log K_{N_0}
1.0	30.00	1.48	28.00	1.45
2.0	23.91	1.38	24.00	1.38
3.0	18.75	1.27	21.00	1.32

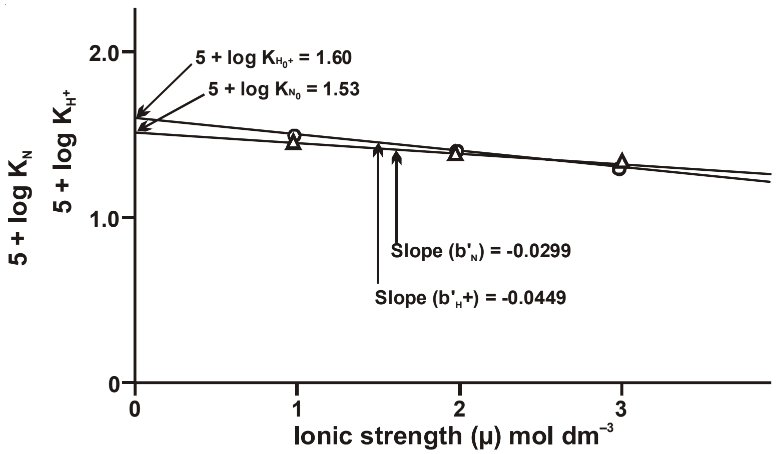


Fig. 2. Hydrolysis of tri-2-ethyl-6-methylaniline phosphate at 97 ± 0.5 ºC

TABLE-4
SPECIFIC ACID CATALYZED ($K_{H_0^+}$) AND SPECIFIC NEUTRAL (K_{N_0}) RATES FOR THE HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT ZERO IONIC STRENGTH AT 97 ± 0.5 ºC

$10^5 \cdot K_{H_0^+}$ (mol dm^{-3} min^{-1})	5 + log $K_{H_0^+}$	b'_{H^+}	$10^5 \cdot K_{N_0}$ (mol dm^{-3} min^{-1})	5 + log K_{N_0}	b'_N
39.81	1.60	-0.0449	33.88	1.53	-0.0299

Thus, the values can be used in the following equations to calculate the acid-catalyzed rate:

$$K_{H^+} = K_{H_0^+} \cdot \exp.b_{H^+} \cdot \mu \tag{2}$$

or, $$K_{H^+}\cdot C_{H^+} = K_{H_0^+}\cdot C_{H^+}\,\exp.b_{H^+}\cdot\mu \tag{3}$$

or, $$5+\log K_{H^+}\cdot C_{H^+} = 5+\log K_{H_0^+}\cdot C_{H^+} + b'_{H^+}\cdot\mu \tag{4}$$

where, K_{H^+} and C_{H^+} are specific rate constant from acid molarity log $K_{H_0^+}$ is the log form of specific acid catalyzed rates and b'_{H^+} = slope of the curve of (Fig. 3), obtained by dividing the slope value 2.303.

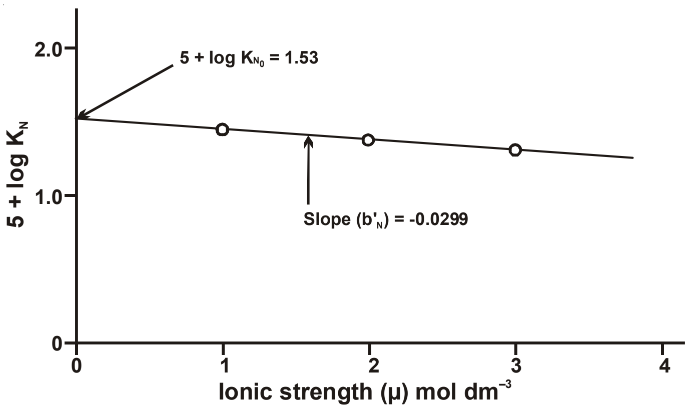


Fig. 3. Hydrolysis of tri-2-ethyl-6-methylaniline phosphate at 97 ± 0.5 ºC

The neutral rates may be represented as follows:

$$K_N = K_{N_0}\cdot\exp.b_N\cdot\mu \tag{5}$$

or, $$\log K_N = \log K_{N_0} + b'_N\cdot\mu \tag{6}$$

or, $$5+\log K_N = 5+\log K_{N_0} + b'_N\cdot\mu \tag{7}$$

where, K_N = neutral rate, $\log K_{N_0}$ = log form of specific neutral rate and b'_N = slope of the curve of obtained by dividing it by 2.303.

The above values have been used to estimate the theoretical rate by following equation:

$$K_e = K_{H^+}\cdot C_{H^+} + K_N \tag{8}$$

These values have been summarized in Table-5. It is clear from the results that there is a fairly good agreement between observed and estimated rates upto 4.0 mol dm^{-3}. The observed deviation in acid solution (5.0 and 6.0 mol dm^{-3} HCl) can be removed by introducing water activity parameter and the above equations, can be shows in Table-5.

TABLE-5
CALCULATED AND OBSERVED RATES FOR THE HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT 97 ± 0.5 ºC

HCl (mol dm^{-3})	pH	$10^5 \cdot K_N$ (mol dm^{-3} min^{-1})	5 + log K_N	$10^5 \cdot K_{H^+} \cdot C_{H^+}$ (mol dm^{-3} min^{-1})	$10^5 \cdot K_{H^+} \cdot C_{H^+}$ (mol dm^{-3} min^{-1})	$10^5 \cdot K_N$ (mol dm^{-3} min^{-1})	$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (Calcd.)	5 + log K_e (Calcd.)	$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (Obsd.)
0.1	1.000	33.65	1.530	3.94	–	–	37.59	1.58	36.16
0.2	0.700	33.42	1.524	7.78	–	–	41.20	1.61	38.52
0.5	0.301	32.74	1.515	18.90	–	–	51.64	1.71	50.01
1.0	0.000	31.63	1.500	35.90	–	–	67.53	1.83	65.30
1.5	-0.176	30.56	1.490	51.13	–	–	81.69	1.91	79.14
2.0	-0.300	29.53	1.470	64.60	–	–	94.13	1.97	89.71
2.5	-0.397	28.43	1.450	76.69	–	–	105.12	2.02	102.31
3.0	-0.477	27.54	1.440	87.56	–	–	115.10	2.06	110.03
3.5	-0.544	26.63	1.430	97.02	–	–	123.65	2.09	120.57
4.0	-0.602	25.73	1.410	105.29	–	–	131.02	2.12	130.68
5.0	-0.699	24.02	1.380	118.71	58.14*	1.76*	69.90	1.84	67.05
6.0	-0.778	22.42	1.350	128.41	29.90*	5.22*	35.12	1.55	34.57

n = o for 0.1 to 4.0 mol dm^{-3} HCl.
n* = 2, 3 respectively for 5.0 and 6.0 mol dm^{-3} HCl.

Acid rates:

$$5 + \log K_{H^+} \cdot C_{H^+} = 5 + \log K_{H_0^+} + \log C_{H^+} + b'_{H^+} \cdot \mu + n \log (a_{H_2O}) \qquad (9)$$

Neutral rates:

$$5 + \log K_N = 5 + \log K_{N_0} + b'_N \cdot \mu + n \log (a_{H_2O}) \qquad (10)$$

where, (a_{H_2O}) is water activity and n is an integer.

The rates calculated by these equations are compared with the observed rates. Now there is a fairly good agreement in the entire acid region (0.1 to 6.0 mol dm^{-3}). Thus acid hydrolysis as well as neutral hydrolysis is governed by both ionic strength and water activity.

Molecularity: The various correlation plot like Hammett plot[14] (0.26), Zucker Hammett plot[15] (0.78), Bunnett plots[16] (ω = 9.17 and ω* = 5.42) and Bunnett Olset plot[17] (ϕ = 1.55); postulates a bimolecular rate of hydrolysis, *i.e.*, the involvement of water molecule as second reaction partner in the slow reaction step, the slopes and Tables 6-8 show the bimolecularity of the reaction.

The Arrhenius parameters[18] at 3.0 and 5.0 mol dm^{-3} HCl, ΔE = 21.51 and 22.42 K cal mol^{-1} frequency factor A = 9.25 × 10^7 and 19.57 × 10^7 s^{-1} and entropy $\Delta S^{\neq}$ = 24.51 and -23.03 e.u. (Table-9).

The above parameters at 3.0 and 5.0 mol dm^{-3} HCl, shows the bimolecular mode of hydrolysis with P–N bond fission[11] and by isokinetic relationship

TABLE-6

HAMMETT PLOT DATA FOR THE RATE OF HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT 97 ± 0.5 ºC

HCl (mol dm^{-3})	$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (Obs.)	5 + log K_e	$-H_0$	$-\log(a_{H_2O})$
1.0	65.30	1.81	0.20	0.017
1.5	79.14	1.90	0.47	0.027
2.0	89.71	1.95	0.69	0.039
2.5	102.31	2.01	0.87	0.053
3.0	110.03	2.04	1.05	0.070
3.5	120.57	2.08	1.23	0.087
4.0	130.68	2.12	1.40	0.107
5.0	67.05	1.83	1.76	0.155
6.0	34.57	1.54	2.12	0.211

TABLE-7

ZUCKER-HAMMETT PLOT DATA FOR THE RATE OF HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT 97 ± 0.5 ºC

HCl (mol dm^{-3})	log C_{H^+}	$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (Obs.)	5 + log K_e
1.0	0.000	65.30	1.81
1.5	0.176	79.14	1.90
2.0	0.300	89.71	1.95
2.5	0.397	102.31	2.01
3.0	0.477	110.03	2.04
3.5	0.544	120.57	2.08
4.0	0.602	130.68	2.12
5.0	0.699	67.05	1.83
6.0	0.778	34.57	1.54

TABLE-8

OLD BUNNETT AND BUNNETT-OLSEN PLOT DATA FOR THE HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE AT 97 ± 0.5 ºC

HCl (mol dm^{-3})	log C_{H^+}	$10^5 \cdot K_e$ (mol dm^{-3} min^{-1}) (obs.)	5 + log K_e	$-H_0$	5 + log K_e − log C_{H^+}	5 + log K_e + H_0	-(-log C_{H^+} + H_0)	-log (a_{H_2O})
	(a)		(b)	(c)	(b-a)	(b-c)	(c-a)	
1.0	0.000	65.30	1.81	0.20	1.81	1.61	0.20	0.017
1.5	0.176	79.14	1.90	0.47	1.72	1.43	0.29	0.027
2.0	0.300	89.71	1.95	0.69	1.65	1.26	0.39	0.039
2.5	0.397	120.31	2.01	0.87	1.61	1.14	0.47	0.053
3.0	0.477	110.03	2.04	1.05	1.56	0.99	0.57	0.070
3.5	0.544	120.57	2.08	1.23	1.54	0.85	0.68	0.087
4.0	0.602	130.68	2.12	1.40	1.52	0.72	0.80	0.107
5.0	0.699	67.05	1.83	1.76	1.13	0.07	1.06	0.155
6.0	0.778	34.57	1.54	2.12	0.76	-0.58	1.32	0.211

(Table-9 and Fig. 4) represents the conjugate acid species hydrolysis with P–N bond fission. Solvent effect and concentration effect also show the reaction to be bimolecular hydrolysis.

TABLE-9
ARRHENIUS PARAMETERS FOR THE RATE OF HYDROLYSIS OF TRI-2-ETHYL-6-METHYLANILINE PHOSPHATE *via* CONJUGATE ACID SPECIES

HCl (mol dm^{-3})	Parameters		Entropy -$\Delta S^{\neq}$ (e.u.)
	Energy of activation (E) (k cal mol^{-1})	Frequency factor (A) (s^{-1})	
3.0	21.51	9.25 × 10^{7}	24.51
5.0	22.42	19.57 × 10^{7}	23.02

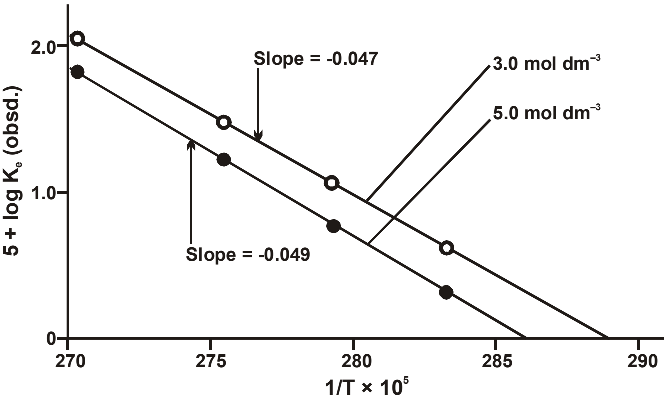
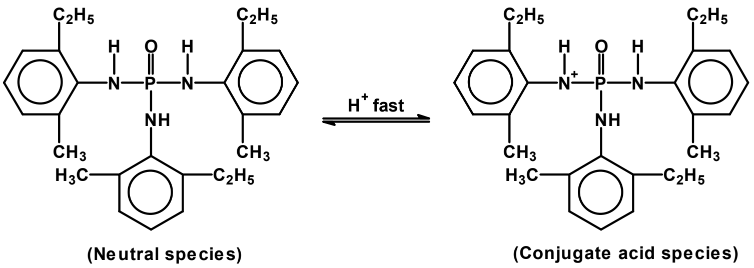


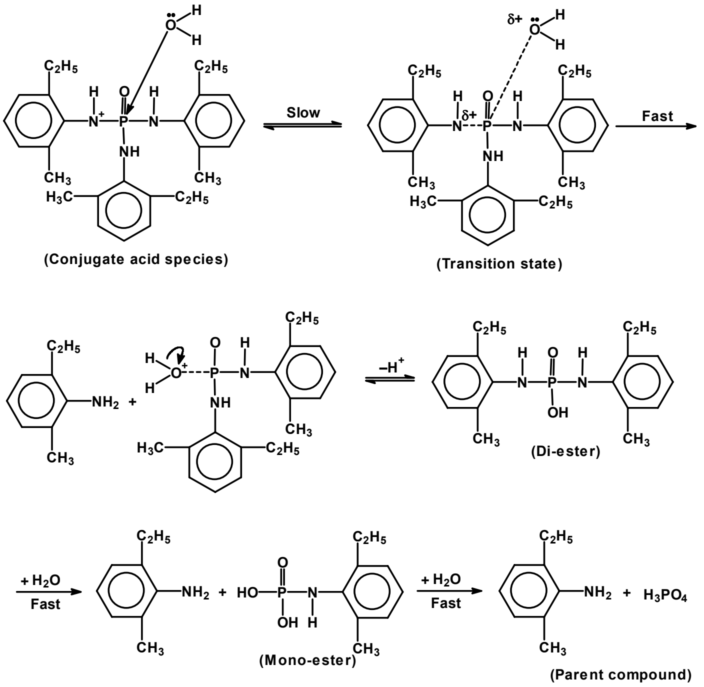
Fig. 4. Arrhenius plot for the rate of hydrolysis of tri-2-ethyl-6-methylaniline phosphate at different temperature

Mechanism: On the basis of experimental investigation, the mecahnism of the acid catalyzed hydrolysis of present tri-ester may be suggested as follows:

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



Bimolecular nucleophilic attack of water molecule on phosphorus S_N^2 (P):



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