Asian Journal of Chemistry; Vol. 28, No. 12 (2016), 2709-2712

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.20077

Kinetic Study of Acidic Hydrolysis of Di-2,3-dichloroaniline Phosphate

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Received: 14 May 2016; *Accepted*: 4 July 2016; *Published online*: 1 September 2016; AJC-18065

Phosphate esters are vital to any living organisms and their hydrolysis plays an important role in many biological processes. In present study acid catalyzed hydrolysis of di-2,3-dichloroaniline phosphate has been carried out in 0.5-7.0 mol dm^{-3} HCl at 80 °C in 30 % (v/v) dioxane-water medium. The pseudo first order rate constants have been determined. The rate of hydrolysis increases with increase in acid molarity up to 4 mol dm^{-3} HCl and after that it decreases. The decrease in rate has been attributed to the effect of water activity. The effect of various parameters such as solvent, substrate concentration and ionic strength on the rate of hydrolysis has been studied to find out the bond fission, molecularity and order of reaction. Bimolecularity of the reaction has been discussed in terms of concepts such as Arrhenius parameters, Zücker-Hammett hypothesis, Bünnett and Bünnett-Olsen's parameters. Kinetic rate data and isokinetic relationship has been employed to suggest bond-fission of the reaction. The probable reaction mechanism *via* conjugate acid species has been proposed.

Keywords: Hydrolysis, Di-2,3-dichloroaniline phosphate, Ionic strength, Bond fission.

INTRODUCTION

Phosphate esters play important roles in many areas of science. Mono- and di-esters are involved in countless biological processes, most prominently the storage and transmission of genetic information involving DNA and RNA [1-3]. Triesters do not occur naturally, but together with related compounds have found widespread use as herbicides and insecticides since the mid-20th century [4]. C-N-P linkage containing phosphate esters exhibit multifaceted applications in modern organic and medicinal chemistry [5-7]. These esters are used as antibacterial, antiviral, antitumor agents and are normally considered as important pharmacological compounds and have received an increasing amount of attention due to their significant biological interests [8]. In addition to this, they also proved their technical importance for industries. Phosphate esters represent an important class of commercial additives used as flame retardants, plasticizers, hydraulic fluids, solvents, extraction agents, antifoam agents, adhesives and coatings for electronic devices [9]. Hydrolysis of phosphate esters is of crucial importance to biological systems, being involved in energy transduction, biosynthesis, control of secondary messengers and regulation of protein function [10]. The hydrolysis of phosphodiesters is especially important in biochemical and medicinal research [11]. In present investigation attempt was made to study the acid catalyzed hydrolysis of di-2,3-dichloroaniline phosphate in dioxane-water medium.

EXPERIMENTAL

Di-2,3-dichloroaniline phosphate was synthesized by Rudert method [12] using 2,3-dichloroaniline and phosphorylating agent phosphorus oxychloride in 2:1 mol ratio in benzene (solvent). The crude product obtained of diester was recrystallized by ammonia and HCl solutions to get a pure sample of diester. Synthesized diester was identified by FTIR spectral and elemental analysis.

All the reactions were carried out at 80 ± 0.5 °C employing 5.0×10^{-4} mol dm^{-3} concentration of the synthesized diester in 30 % (v/v) dioxane-water medium. The constant ionic strength was maintained by appropriate mixture of HCl and NaCl. All the chemicals used were of AR grade. The progress of kinetic study of di-2,3-dichloroaniline phosphate was made by systronics spectrophotometer (model no.105) using Allen's modified method [13] which involves the estimation of inorganic phosphate.

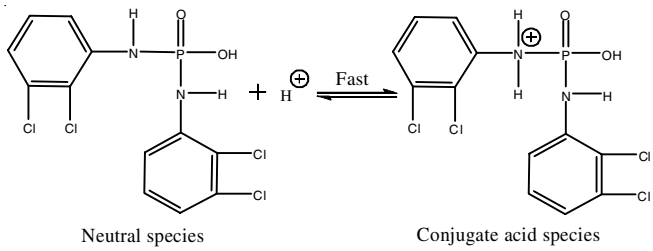
RESULTS AND DISCUSSION

Hydrolysis of di-2,3-dichloroaniline phosphate was carried out at 80 °C in the range of 0.5 to 7.0 mol dm^{-3} HCl in 30 % (v/v) dioxane-water medium. The pseudo-first order rate constants were obtained at different acid molarities are summarized in Table-1. From the results, it is found that the rate of hydrolysis of di-ester increases with the increase in acidities up to 4 mol dm^{-3} HCl. The maximum rate at 4 mol dm^{-3}

TABLE-1
ESTIMATED AND EXPERIMENTAL RATES FOR THE HYDROLYSIS OF DI-2,3-DICHLOROANILINE PHOSPHATE *via* CONJUGATE ACID AND NEUTRAL SPECIES

HCl (mol dm^{-3})	$k_H^+ \cdot C_H^+ \times 10^3$ (min^{-1})	$k_N^+ \times 10^3$ (min^{-1})	-log $(a_{H_2O})^n$	$k_e \times 10^3$ (min^{-1}) Estd.	$k_e \times 10^3$ (min^{-1}) Expt.	3 + log k_e Estd.	3 + log k_e Expt.
0.5	2.83	2.07	–	4.90	5.30	0.69	0.72
1.0	6.22	2.71	–	8.93	9.38	0.95	0.97
1.5	10.26	3.54	–	13.80	13.83	1.14	1.14
2.0	15.03	4.62	–	19.65	19.89	1.29	1.30
2.5	20.65	6.04	–	26.69	26.71	1.43	1.43
3.0	27.23	7.89	–	35.12	35.14	1.55	1.55
3.5	34.91	10.30	–	45.21	45.21	1.66	1.66
4.0	43.86	13.46	–	57.32	57.33	1.76	1.76
4.5	54.23	17.58	(0.130)	71.81	52.94	1.72	1.72
5.0	66.22	22.96	$(0.155)^2$	89.18	44.41	1.64	1.65
5.5	80.06	30.00	$(0.181)^{2.5}$	110.06	36.89	1.58	1.57
6.0	95.98	39.17	$(0.211)^3$	135.15	31.50	1.50	1.50
7.0	135.24	66.83	$(0.279)^4$	202.07	15.47	1.19	1.19

HCl was ascribed to complete conversion of the substrate into its conjugate acid species (**Scheme-I**). Further rise in acidities decrease the rate constant. The decrease in rate constant was attributed to the decrease in the concentration of attacking nucleophile (water) taking part in the reaction and variation in water activity.



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

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. 1). 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 effect. 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.

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-Hückle equation [14].

$$k_e = k_H^+ \cdot C_H^+ + k_N \quad (1)$$

In the above equation the terms k_e, k_H^+ and k_N are experimental rate constants, the specific acid catalyzed rates and specific neutral rates at that ionic strength respectively. Specific acid catalyzed rates (k_H^+) were then converted into acid rates ($k_H^+ \cdot C_H^+$) as:

$$k_H^+ \cdot C_H^+ = k_{Ho}^+ \cdot C_H^+ \cdot \exp b'^+_H \cdot \mu \quad (2)$$

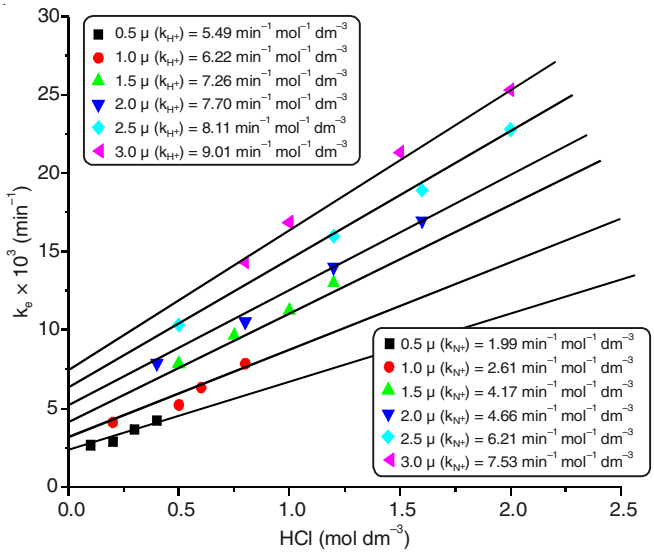


Fig. 1. Rate constant *vs.* acid molarity for acid catalyzed hydrolysis of di-2,3-dichloroaniline phosphate at constant ionic strength

where for HCl, μ and C_H^+ are of the same value. The slope of the linear curve is b'^+_H, which is equal to $b'^+_H/2.303$ and intercept on the log rate axis is 3 + log k_{Ho}^+ (Fig. not shown). The sum of neutral and acid rates agrees well with the experimentally observed rates (Table-1) up to 4 mol dm^{-3} HCl. In the region of 0.5 to 4 mol dm^{-3} the rate law is calculated by equation:

$$k_e = 5.15 \times 10^{-3} \cdot C_H^+ \exp. (0.082 \times 2.303) \cdot \mu + 1.59 \times 10^{-3} \exp. (0.232 \times 2.303) \cdot \mu \quad (3)$$

The lowering in rates in 4.5, 5.0, 5.5, 6.0 and 7.0 mol dm^{-3} HCl can be explained by considering water activity as an additional parameter represented as:

$$k_e = k_{Ho}^+ C_H^+ \exp. b'^+_H \cdot \mu (a_{H_2O})^n + k_{No} \exp b'_N \cdot \mu (a_{H_2O})^n \quad (4)$$

where n is an integer and $(a_{H_2O})^n$ is water activity [15]. Hence the rate laws beyond 4.0 mol dm^{-3} HCl were calculated employing the Bronsted-Bjerrum equation [16]:

$$k_e = 5.15 \times 10^{-3} \cdot C_H^+ \exp. (0.082 \times 2.303) \cdot \mu (a_{H2O})^n + 1.59 \times 10^{-3} \exp. (0.232 \times 2.303) \cdot \mu (a_{H2O})^n \quad (5)$$

The revised estimated rates agree well with the experimentally observed rates (Table-1). It is clear from the above result that di-2,3-dichloroaniline phosphate in acid solution occurs *via* both conjugate acid and neutral species and their rates are subjected to both ionic strength and water activity.

Molecularity of reaction: Arrhenius parameters [17] (figure not shown) determined for the hydrolysis at 3.5 mol dm^{-3} HCl are activation energy (E_a) = 16.01 kcal mol^{-1}, frequency factor (A) = 3.72×10^8 S^{-1} and entropy ($-\Delta S^{\neq}$) = 21.66 e.u. The magnitude of the Arrhenius parameters falls in the range of bimolecular reaction. Bimolecular nature of reaction is further supported by plots of Hammett [18] (0.67), Zücker-Hammett [19] (1.33) and Bünnett [15] (w = 7.95, w* = 2.45). Bünnett-Olsen [20] parameter (ϕ = 1.40 which is greater than 0.58) (plots not shown) suggested that water activity is playing an important role in deciding the rate at higher acidic concentration.

Effect of solvent: Table-2 shows that the rate constant value gradually increases with the gradual addition of 1,4-dioxane. Dioxane is regarded as a polar aprotic solvent. Dioxane increases the concentration of conjugate acid species resulting in the increase rate. The effect of solvent on rate of hydrolytic reaction indicates the transition state in which charge is dispersed. This is accordance with Chanley's observation [21].

TABLE-2
SOLVENT EFFECT RATE DATA FOR ACID CATALYZED HYDROLYSIS OF DI-2,3-DICHLOROANILINE PHOSPHATE

HCl (mol dm^{-3})	Percentage of solvent (1,4-dioxane)	$k_e \times 10^3$ (min^{-1})
3.5	20	43.01
	30	45.21
	40	49.36
	50	53.12
	60	57.66

Effect of substrate concentration: For determination of kinetic order, a series of kinetic runs with different substrate concentrations (2.5, 5 and 8 × 10^{-4} mol dm^{-3}) have been performed at 3 mol dm^{-3} HCl in 30 % (v/v) dioxane-water medium at 80 °C and obtained first order rate constants, k_e (57, 57.33, 57.20 min^{-1}). The results show that the rate constants are independent of substrate concentrations. Thus the solvolytic reaction proceeds *via* pseudo first order reaction.

Bond-cleavage of reaction: Bimolecular nature of hydrolysis of di-2,3-dichloroaniline 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-3. The isokinetic relationship plot ($-\Delta S^{\neq}$ *vs.* E) shows point of di-2,3-dichloroaniline phosphate is collinear with other diesters which are known to undergo bimolecular hydrolysis *via* P-N bond fission (Fig. 2).

Mechanism: On the basis of experimental results, the probable reaction mechanism of the acid-catalyzed hydrolysis of di-2,3-dichloroaniline phosphate *via* conjugate acid species may be as shown by **Schemes I** and **II**.

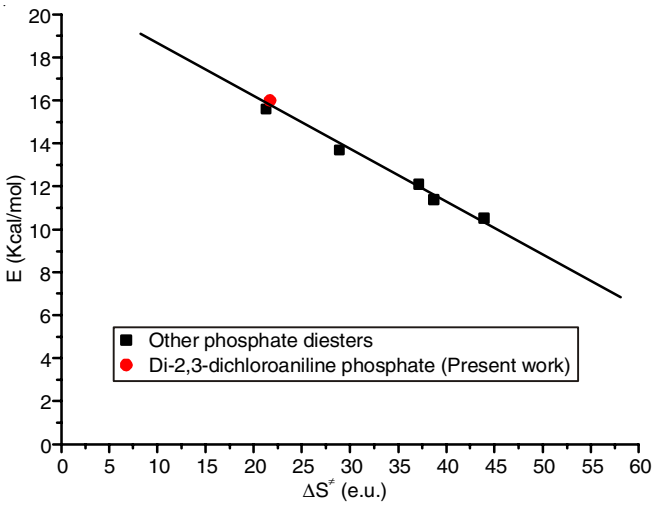
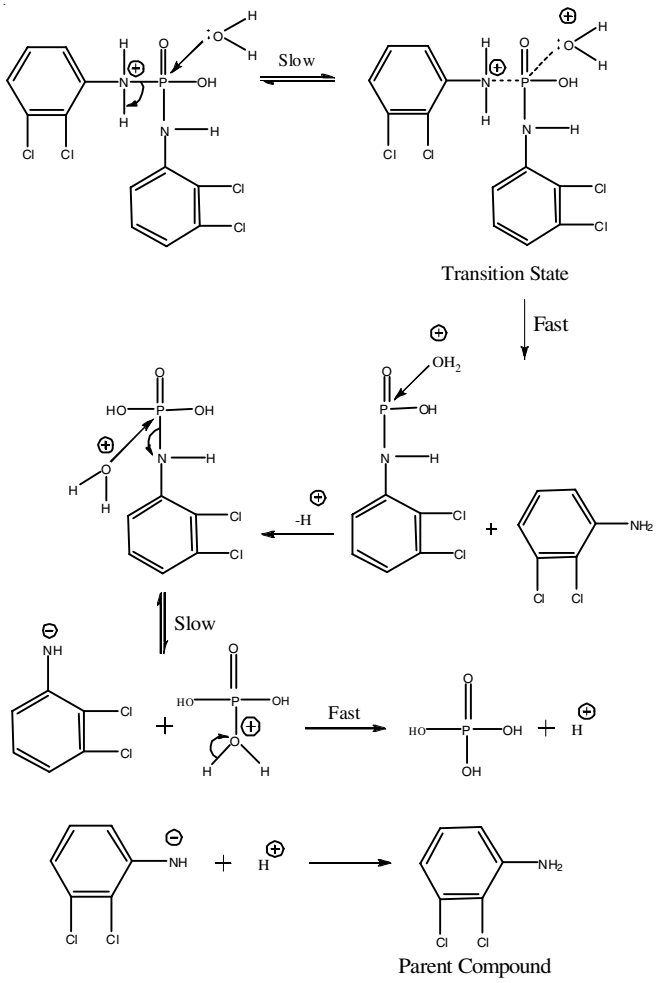


Fig. 2. Isokinetic relationship plot for the hydrolysis of some phosphate di-esters



Scheme-II: Bimolecular nucleophilic attack of water on phosphorus *via* conjugate acid species $S_N^2(P)$

Conclusion

Acidic hydrolysis of di-2,3-dichloroaniline phosphate in 0.5 to 7.0 mol dm^{-3} HCl has been found to proceed *via* neutral and conjugate acid species. The acid catalyzed hydrolysis is subjected to positive effect of ionic strength. Different parameters such as Arrhenius, Bünnett, Bünnett-Olsen and Hammett, Zücker-Hammett hypothesis *etc.* supported the

TABLE-3
COMPARATIVE KINETIC RATE DATA FOR HYDROLYSIS OF SOME DIESTERS *via* CONJUGATE ACID SPECIES

Phosphate diesters	HCl (mol dm^{-3})	E (Kcal/mol)	$-\Delta S^{\neq}$ (e.u.)	Molecularity	Bond fission
2-Methyl-5-nitroaniline phosphate	6.0	10.52	43.92	2	P-N
o-Toluidine phosphate	1.0	11.4	38.70	2	P-N
Cyclohexylamine phosphate	3.0	12.1	37.11	2	P-N
2-Chloroaniline phosphate	3.0	13.7	28.90	2	P-N
m-Toluidine phosphate	3.0	15.6	21.29	2	P-N
2,3-Dichloroaniline phosphate	3.5	16.0	21.68	2	Present work

bimolecular nature of hydrolysis. Comparative isokinetic relationship plot supported the P-N bond fission. The probable $S_N^2(P)$ mechanism was suggested for the hydrolysis *via* conjugate acid species.

ACKNOWLEDGEMENTS

The authors are thankful to Head, School of Studies in Chemistry, Pt. Ravishankar Shukla University, Raipur (C.G.) for kind support and providing research facilities.

REFERENCES

1. W.W. Cleland and A.C. Hengge, *Chem. Rev.*, **106**, 3252 (2006).
2. A.C. Hengge, in ed.: J.P. Richard, Advances in Physical Organic Chemistry, Academic: New York, pp. 40-49 (2005).
3. J.K. Lassila, J.G. Zalatan and D. Herschlag, *Annu. Rev. Biochem.*, **80**, 669 (2011).
4. J.R. Mora, A.J. Kirby and F. Nome, *J. Org. Chem.*, **77**, 7061 (2012).
5. A. Mucha, P. Kafarski and L. Berlicki, *J. Med. Chem.*, **54**, 5955 (2011).
6. M. Serpi, R. Bibbo, S. Rat, H. Roberts, C. Hughes, B. Caterson, M.J. Alcaraz, A.T. Gibert, C.R.A. Verson and C. McGuigan, *J. Med. Chem.*, **55**, 4629 (2012).
7. A.K. Kanduluru and S.R. Cirandur, *Phosphorus Sulfur Silicon Rel. Elem.*, **191**, 719 (2016).
8. S.J. Hecker and M.D. Erion, *J. Med. Chem.*, **51**, 2328 (2008).
9. J. Andresen and K. Bester, *Water Res.*, **40**, 621 (2006).
10. S.C.L. Kamerlin and J. Wilkie, *Org. Biomol. Chem.*, **5**, 2098 (2007).
11. P. Gomez-Tagle and A.K. Yatsimirsky, *J. Chem. Soc., Dalton Trans.*, 2663 (2001).
12. P. Rudert, *J. Chem. Soc. (A)*, 323 (1893).
13. R.J.L. Allen, *Biochem. J.*, **34**, 858 (1940).
14. J.E. Lafler and E. Grunwald, The Rate and Equilibria of Organic Reaction, Wiley, New York, p. 286 (1963).
15. J.F. Bünnett, *J. Am. Chem. Soc.*, **83**, 4978 (1961).
16. P.W.C. Branard, C.A. Bunton, D. Kellemann, M.M. Mhala, C.A. Vernon and V.A. Welch, *J. Chem. Soc. B*, 227 (1966).
17. S. Arrhenius, *Z. Phys. Chem.*, **4**, 226 (1889).
18. L.P. Hammett, Physical Organic Chemistry, McGraw Hill: London, p. 335 (1940).
19. L. Zücker and L.P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).
20. J.F. Bünnett and F.F. Olsen, *Can. J. Chem.*, **44**, 1917 (1966).
21. J.D. Chanley and E.J. Feageson, *J. Am. Chem. Soc.*, **80**, 2686 (1958).