Acid-Promoted Hydrolysis of m-Cl-Phenyl Phosphorotriamidate leading to its Highly Basic Nature by Kinetic Means

HARISH KUMAR AMB* and SHASHI PRABHA

*Department of Chemistry, Govt. P.G. College, Guna, India.
Retd. Professor, School of Studies in Chemistry, Jiwaji University Gwalior - 474011, India.
*Corresponding author E-mail : harishkumar.hk559@gmail.com

ABSTRACT

Hydrolysis of m-Cl-Phenyl Phosphorotriamidate has been performed in the acid range, 0.01to 7.0M –HCl,in 12%AcoH-H_2O (v/v) at 98($\pm$0.5)°C. The continuous second-order rate rise with the absence of a rate maximum in the entire acid range is significant, leading to its highly basic nature. In this respect, it differs from other related(o-Cl-Ph-&p-Cl-Ph-) members of the phosphorotriamidate group. The salt effect variable study leads to the presence and reactivity of the two major reactive species with the Neutral Species(I) working in the entire acid range; while the Conjugate acid form(II) was observed operating between 4.0-7.0M HCl region only. Both uni-and bi-molecular mechanisms for the two reactive forms with P-N bond fission have been decided for the C-N-P ester. The hydrolysis is shown to be decreased by the action of the series of the nucleophilic reagents and I'shows the optimum effect here. Role of a chloro-group in the unusual meta position in each aryl matix during hydrolysis was particularly the important feature of this study.

Key words : Hydrolysis, Neutral Species, Conjugate acid species, Basicity.

INTRODUCTION

Organic phosphoramidate have been widely utilized for synthetic[1,2] work, especially for the synthesis of pyrophosphates. These compounds may also function as fireproof materials[3] (e.g. phosphoric aniline diamide); as polymers [4,5] and co-polymers (Aromatic araliphatic compounds based on Phosphoric acid and Thiphosphoric acid amides). The latter are then suitable for making films, membranes and fibers etc. Organic phosphoramidates even have the potential for their function as the harmful insecticides,[6] while others may act as very useful drugs for the treatment[7] of AIDS and Cancer etc.

EXPERIMENTAL

The m-Cl-Phenyl Phosphorotriamidate had been synthesized by refluxing for ca.8 hrs. with morpholine as catalyst. The ratio of reactants such as m-Cl-Aniline,$POCl_3$ and Morpholine was 3:1:3 in a dry benzene medium. A creamish-solid was obtained after total refluxing period and this solid after treatment with $CHCl_3$, H_2O and acetone, a white substance with yellowish tinge was formed, having a sharp m.p.251-253°C. Its purity was checked with tlc, and the single sharp spot was observed as desired. It was confirmed as the m-Cl-phenyl phosphorotriamidate on the basis of quantitative P content estimation.

Kinetic study of acid-catalysed hydrolysis(98±0.5)°C of m-Cl-Phenyl phosphorotriamidate was made using Allen's modified method. During the kinetic study the optical density was measured with help of Systronics-118: UV-Vis. spectrophotometer. Concentration of the compound was maintained as 8.0×10^{-4} M throughout the study, except for concentration effect study.

RESULTS AND DISCUSSION

m-Cl-Phenyl Phosphorotriamidate, a C-N-P bearing ester, has been synthesised in this chemical laboratory and examined for its hydrolysis in 12%AcOH-H_2O medium, in the acid range 0.01 to 7.0 M-HCl, at 98(±0.5)°C.The estimated second-order rate coefficients have been presented in Table I, showing their general trend, in the entire acid region examined. Allen's modified method[8] has been used to quantitatively determine the extent of hydrolysis on the basis of phosphorus liberated as H_3PO_4 component. At 4.0 M-HCl and onwards, the observed rate coefficients rise continuously till 7.0 M-HCl under the common set of reaction conditions. The acid-rate profile (not shown) showed that there is a plateau in the acid range, 0.3 M to 3.0 M-HCl. After this, the rates show a steep rise without involving any rate maximum in this higher zone of acid concentrations. This pattern of rates reflects the kinetic behaviour of strongly basic compounds, the amides[9,10] in this molecule as well.

In order to determine the presence as well as the contribution of the reactive forms, the Neutral

Table 1: Observed (12% AcOH-H_2O) and Calculated Rate Coefficients for the Hydrolysis of m-Cl-Phe nyl Phosphorotriamidate in the acid range at 98(±0.5)°C

S. No.	HCl (M)	$10^1 k_N$ $M^{-1} min^{-1}$	$10^1 k_H^+ \cdot C_H^+$ $M^{-1} min^{-1}$	10^1 ke calcd. $M^{-1} min^{-1}$	10^1 ke obsd. $M^{-1} min^{-1}$
1	0.1	1.50	-	1.50	1.02
2	0.3	1.50	-	1.50	4.04
3	1.0	1.50	-	1.50	2.23
4	2.0	1.50	-	1.50	1.74
5	3.0	1.50	-	1.50	1.52
6	4.0	1.50	1.71	3.21	3.55
7	5.0	1.50	2.13	3.63	9.45
8	6.0	1.50	2.57	4.07	14.28
9	7.0	1.50	2.99	4.49	17.60

Table 2: Arrhenius Parameters for the Hydrolysis (0.1 M-HCl) of m-Cl-Phenyl Phosphorotriamidate

Energy of Activation $E\alpha$	Frequency Factor 'A'	Entropy of Activation $\Delta S^{\neq}$	Enthlapy of Activation $\Delta H^{\neq}$	Free energy of Activation $\Delta G^{\neq}$
154.39 KJ mol^{-1}	3.47×10^{19} M^{-1}Sec^{-1}	+37.55 e.u.	151.32 KJ mol^{-1}	93.08 KJ mol^{-1}

electrolyte effect study[11] had been made keeping the ionic strengths (µ) as 1.0, 2.0 and 3.0, using suitable compositions of both LiCl and conc. HCl. In Fig.1, three linear curves are seen to be formed, with different slopes (K_H^+) but making a common intercept (K_N) on the Y-axis. Using the IInd empirical term[12] of Debye Hückel equation correlation (i) is used to calculate the total rates for the contributory reactive species :

Thus, $k_e = k_N^+ \ k_H^+ . C_H^+$ ...(i)

Also, $k_N = k_{No} \times e^b N^\mu$ ...(ii)

Equation (ii) is simplified, as Fig.1 shows that the Neutral species (I) makes a fixed contribution, so that:

$k_N = k_{No} = 1.50 \times 10^{-1} \ M^{-1}min^{-1}$ ...(III)

Further : $k_H^+ . C_H^+ = k_{Ho}^+ . C_H^+ . e^b{}_H^+ . \mu$ ...(iv)

where, k_H^+, C_H^+ and k_{Ho}^+ represents the acid-catalysed rates via the Conjugate acid species(II), the concentration of the H⁺ -ions and the rates via the Conjugate acid species(II) at zero ionic strength only.

Logarithmically, equation (iv) is represented as

$\log k_H^+ . C_H^+ = \log k_{Ho}^+ . \log C_H^+ + . b'{}_H^+ . \mu$ ...(v)

It may be seen that the Neutral species (I) makes a constant contribution in the acid region, particularly between 0.01 to 3.0 M-HCl (Table I).
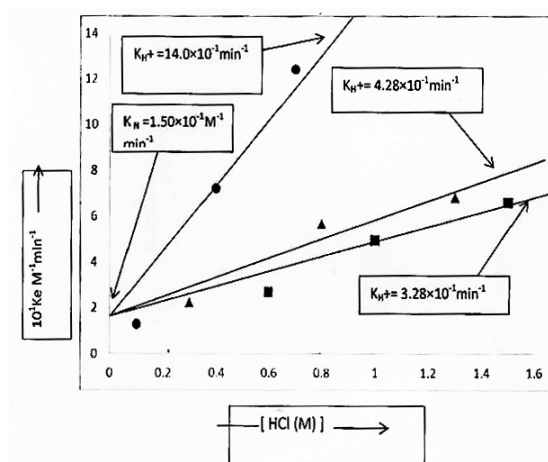

Fig. 1: Hydrolysis of m-Cl-Phenylphosphorotriamidate at constant ionic strengths in 12% AcOH-H2O(v/v) at 98 (±0.5)°C

The acid-catalysed rate (k_H^+) at zero ionic strength (1+ log k_{Ho}^+ =0.63) is obtained (Fig.not shown), while b'$_H^+$ =0.00. Using all these parameters in equation (v), the rates via Conjugate acid species(II) were determined at each acid molarity separately. Table I includes this data, and it may be noticed that there is a similarity between the calculated and the observed rate coefficients via the Neutral form(I) in 0.1-3.0 M-HCl region only. Between 4.0 M to 7.0 M-HCl, both the Neutral and the Conjugate acid (II) species are both found to contribute toward the overall rates of hydrolysis. However, the differences between k_e observed and k_e calculated values are due to the exceptional basic character shown by the m-Cl-phenyl phosphorotriamidate under observation. This particular feature makes it significant for the kinetic study in particular.

In higher acid media(1.0 M-HCl and above) Hammett[11] plot(slope=0.53) failed to give any concrete result. Normal Bunnett correlations[13] (Figs. not included) giving w = +3.0 and w' = 1.90 are not satisfactory (see later) in this case. Bunnett and Ölsen plot[13] drawn between (logk_e +H_o) versus [(log C_H^+ + H_o)] gives a slope, ϕ, as + 0.68. This favours the role of water both as a nucleophilic as well as a proton –transferring agent. The latest correlation[14] till date in strong acid media, the Yates and McClelland plot(based on modified-Hammett plot : m= +0.285 and–log aH_2O data) gives slope, r =3.03. Both 'r' and 'w' giving identical (3.0) values strongly favour the participation of minimum three water molecules during the hydrolysis.

A simple but specific correlation (rates versus acid molarities) suggested by Bunnett for highly basic compounds was drawn (Fig. not included) giving a new slope, w¢ = 4.69. This value suggests that water acts as a second reactant, in the rate-determining step of the present hydrolysis. The slope of the special Bunnett plot thus leads to the role of around four to five water molecules, during the hydrolytic reaction. This value strongly supports the recently identified minimum sized-but stable hexahydrated-proton species[15], [H⁺(H_2O)$_6$] to bring about protonation, in spite of having a very short span of life.

The Arrhenius parameters (Table II) were determined from rate data determined at three different

(98, 90 & 80°C) temperatures at 0.1 M-HCl in 12%AcOH-H_2O medium. The well-known Arrhenius equation was thus used leading to the suitable Arrhenius parameters. The high energy of activation[11], E_a and the high collision factor (A) support respectively, a uni- and a bi-molecular route of hydrolysis in this case. The entropy of activation ($\Delta S^{\neq}$) being a +ve quantity (Table II) also supports the unimolecular mode of hydrolysis. Both $\Delta H^{\neq}$ and $\Delta G^{\neq}$ have been observed to be higher and positive favouring hydrolysis of the triamidate at the boiling water temperature i.e. at 98(±0.5)°C.

Effect of change of medium from 12% to 79% AcOH-H_2O medium at 2.0 M-HCl shows an increase in rates from 1.74×10^{-1} M^{-1} min^{-1} to $10.27\times10^{-1}M^{-1}$ min^{-1} favouring a transition state with charges created in it, possible only via the Neutral species(I) of the phosphorotriamidate under observation. The decrease of ε of the medium with rise in AcOH %age favours protonation of the substrate i.e. the phosphorotriamidate itself.

Concentration effect study at 3.0 M-HCl favours second-order for acid hydrolysis. The second reactant, H_2O, being in much large excess, the study suggests the overall hydrolysis belongs to the pseudo-first order type, however. They also indicate the compound to undergo direct scission. This mainly applies to the Conjugate acid species (II) of the phosphorotriamidate mainly.

Parent amine effect study at 1.0 M-HCl in 12%AcOH-H_2O medium only slightly affects the rates of hydrolysis, so that during the progress of hydrolysis when it is being liberated its role as a nucleophile is also not very significant. The effect of other nucleophilic reagents(Cl', Br', etc.) at 4.0M-HCl (12% AcOH-H_2O) at 98°C, gave the following order of reactivity:

Nucleophilic
reagents: I'   < Cl'   < F'   < Br' < $H_2\ddot{O}$
10^1ke M^{-1}
min^{-1} :   0.52 1.10   1.80 1.98   3.55

All the above nucleophilic reagents (0.1 M) result in a decrease in the rates of hydrolysis and the iodide ions show the least reactivity towards the phosphorotriamidate.

The nature of the P-N bond fission was confirmed by applying an azo-dye[16] test. During the progress of acid hydrolysis, the parent amine being released gave a +ve test suggestsing P-N bond fission to occur. Other comparative kinetic and thermodynamic data (not included) for related C-N-P members also supported P-N bond fission only. The progress of hydrolysis of the phosphorotriamidate is based on its highest rates shown in the form of comparative kinetic data of the total series as under :

	Monoamidate	Diamidate	Triamidate
Compounds	1(m-Cl-Ph-NH-)	2(m-Cl-Ph-NH-)	3(m-Cl-Ph-NH-)
10^2 M^{-1} min^{-1}	20.43	27.78	35.50
Medium	20% AcOH-H_2O	10%AcOH-H_2O	12%AcOH-H_2O

The above comparison at 4.0 M-HCl shows that the triamidate does not hydrolyse via the formation of either the Mono- or the Di-amidate of the corresponding type. The hydrolysis thus, involves simultaneous scission of all the three subsd.-aryl units of the phosphorotriamidate, under observation.

CONCLUSION

Kinetic study performed during hydrolysis shows that m-Cl-Phenyl phosphorotriamidate undergoes hydrolysis via two reactive forms, Neutral Species (Bimolecular) and Conjugate acid (Uni- and Bi- molecular) with P-N bond fission, as shown below :

Mechanism (1): $S_N2(P)$: Bimolecular hydrolysis of m-Cl- phenyl phosphorotriamidate via the Neutral Species(I) in the entire (0.01 – 7.0 M-HCl) acid region with P-N bond fission:


(I) Neutral Species

T.S. (with Creation of charges)

m-Cl-Aniline   Orthophosphoric Acid
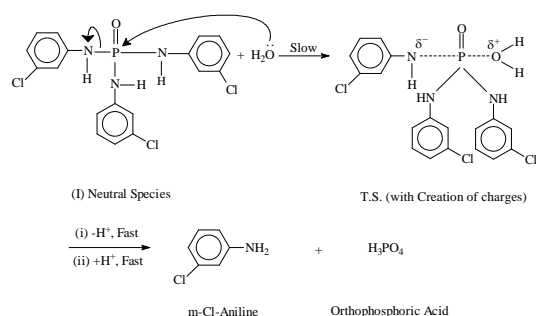
Mechanism(2) : S$_N$1(P) : Unimolecular mechanism of hydrolysis via the Conjugate acid Species (II) between 4.0-7.0 M-HCl

(a)   Formation of Conjugate acid Species(II) by a fast pre- equilibrium proton transfer step :

(b)   Simultaneous cleavage of all the three protonated units in the AcOH-H$_2$O (12%) medium :

(a)

Conjugate Acid Species(II)

(b)

Conjugate Acid Species(II)
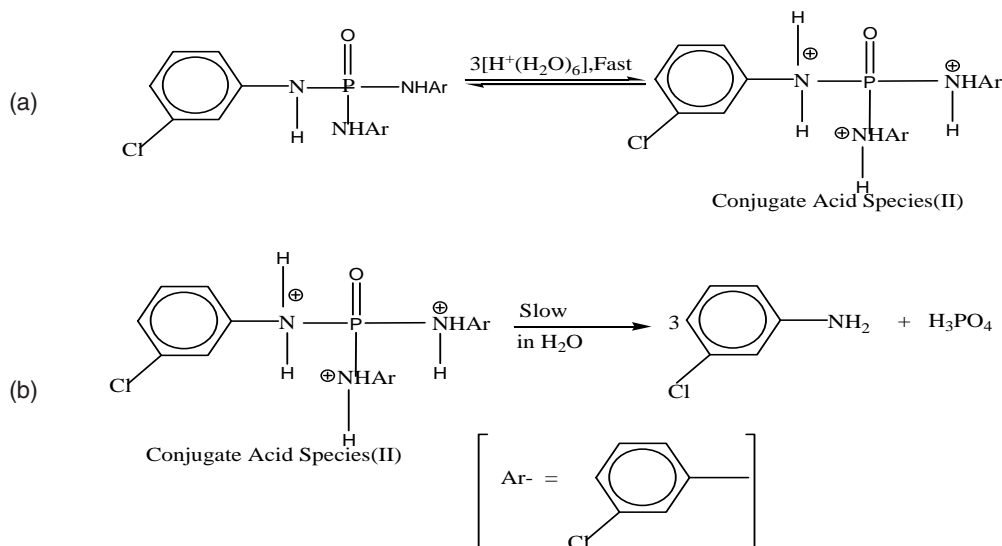
Mechanism (3): S$_N$2 (P) : Bimolecular hydrolysis via the Conjugate acid Species (II) between 4.0-7.0 M, HCl :

(a)'   Formation of Conjugate acid species(II) of m-Cl-Phenyl Phosphorotriamidate: Same as given in 2(a) earlier
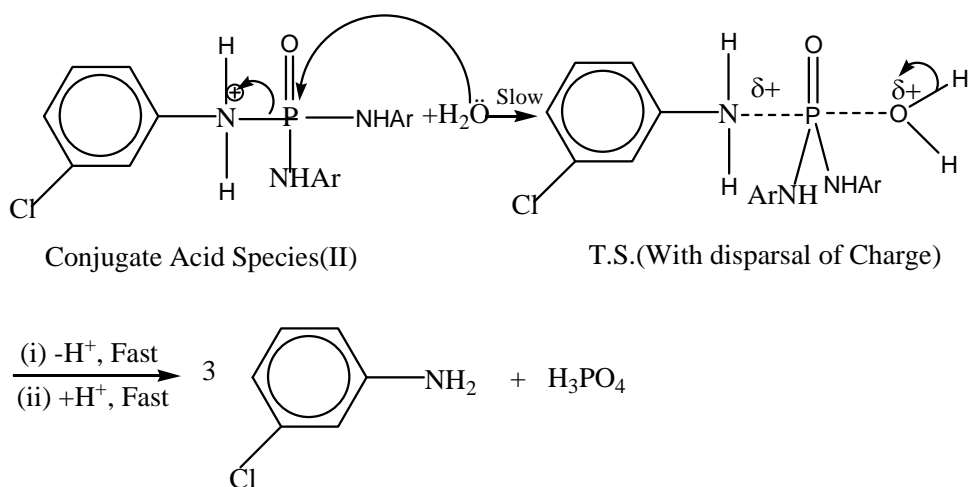
Conjugate Acid Species(II)   T.S.(With disparsal of Charge)

REFERENCES

1. (a) Clark, V.M.; Kirby, G. W; and Todd ,A., *J.Chem.Soc.*, **1957**,1497
    (b) Chambers, R.W.; Shapiro, P. and Kurkov V., *J. Am. Chem. Soc.*, **1960,** *82*, 970

2. (a) Toy,D.F.Arthur and Eilers, L. Kenneth, U.S. Patent 3937765, (2009);
    (b) Shejwalkar,Pushker; Nigam, P.; Rath and Bauer, B.Eike, *Molecules*, **2010,** *15*, 2631-2650
    (c) Delley, J.Richard, O'Donoghue, C. Ann Marie and Hodgson, R.W. David*, J.Org.Chem.*, **2012**,*77* ,5829-5831
    (d) Helge Klare, J örg M. Neudorfl and Beilstein, Bernd Goldfuss, *J. Org. Chem.*, **2014**, *10*, 224-236.

3. Kobayashi Etsuro, *Bull. of the Chem. Soc. of Japan*, **1973**, *46*,183-186

4. Kobayashi, E.; Zasshi, Kogyo Kagaku, **1971**,*74*, 1780

5. (a) Menahem A.Kraus, Moshe A.Frommer, Mara Nemas and Rodika Gutman, U.S. Patent (19); **4**, 233, 434; Nov.11, (1980)
    (b) James L. Bertram and William Davis, U.S. Patent (19); **4**, 481, 347; Nov.6 (1984).

6. Carr,Russell L.; Dail,Mary Beth, Chambers, Howard W. and Chambers ,Janice E., *J. Toxicol., Hindawi Publ. Corpn.*, *Volume 2015*, Article ID 470189, 5 pages.

7. (a) Cohen, M. and Westhimer, F.M., *J. Am. Chem. Soc.*, **1952**, *74*,4387
    (b) Moriguchi, T.; Asai, N.; Okada, K.; Scio, K.; Sasaki ,T. and Sekine, M., *J. Org. Chem.*, **2002**, *67*, 3290

8. Allen,R.J.L.*, Biochem. J.*, **1940**,*34,* 858

9. Edward, J.T. and Meacock, S.C.R, *J. Chem. Soc.,* **1957**,2000

10. Rosenthal, D. and Taylor, T.I., *J. Am. Chem. Soc.*, **1957**, *79*, 2684

11. Laidler K.J, Chemical Kinetics, Third ed., Harper & Row Publishers, New York, pp.2, 24-25, 183, 202-203 (1987).

12. Bailley, M.C., *Bull. Soc. Chim. Fr.*, **1942**, 340-405

13. Bunnett, J.F., *J. Am. Chem. Soc.*, **1961**, *83*, 2686

14. .Yates, K. and McClelland, R.A., *J. Am. Chem. Soc.,* **1967**,*89*, 2686

15. Jiang,J.C.; Wang,Y.S.; Chang,H.C.; Lin,S.H.; Lee,Y.T.; Schatteburg,G. Niedner, *J. Am. Chem. Soc.,* **2000**,*122,* 1398-1410

16. Furniss B.S, Hannaford A.J, Smith P.W.G. and Tatchell A.R., Vogel's T.B. of Practical Organic Chemistry, Fifth ed., Addison-Wesley Longman Ltd., England, pp.166-168,199-215 (1998).