Asian Journal of Chemistry Vol. 19, No. 4 (2007), 2672-2678

Synthesis and Antimicrobial Activity of Disubstituted Arylphosphoric Diamide

SHASHI PRABHA* and AMITA SAXENA
School of Science in Chemistry, Jiwaji University, Gwalior-474 001, India

Synthetic *o*-nitro-*p*-chloro-phenyl phosphoric diamide hydrolyses *via* neutral and the conjugate acid species, with two rate maxima (2 and 5 M HCl) at 40 (± 0.5)°C in 12 % DMSO-H_2O mixture. Specific acid catalysis bimolecular mode and P-N bond fission, all leading to two mechanistic routes of hydrolysis have been established. The special feature is the intervention of the corresponding monoester during acid hydrolysis. Antifungal activity of C-N-P ester has been observed for *C. albicans* and *C. neoformans*.

Key Words: Phosphoric diamide, Bimolecular and Antifungal activity.

INTRODUCTION

Aryl phosphoramidates[1] (or phosphoric amides) have gained entry as flame-proofing agents[2], petroleum additives[3], rust preventives, agrochemicals, defence-related chemicals, insecticides[4], *etc*. during the 20th century. They undergo both[5] electrophilic as well as nucleophilic catalysis and are also known to possess synthetic utility[6].

EXPERIMENTAL

o-Nitro-*p*-chloroaniline with phosphorus oxychloride (4:1) in the presence of morpholine (0.01 mL) in dry benzene, on refluxing at 110 ± 5°C for nearly 7 h and later cooling, gave a yellowish-brown sticky mass, which on purification with benzene gave a yellow solid. It was quantitatively tested[7] for phosphorus (m.p. = 160°C and % P = 7.62).

RESULTS AND DISCUSSION

The present disubstitued phenyl phosphorodiamidate (or phosphoric diamide) was studied for its hydrolytic stability in acid (0.1-7.0 M, HCl) medium. The first-order rates have been calculated and the hydrolysis was followed spectrophotometrically using Allen's modified method[7]. With the rise in acid molority, two rate maxima[8] have been observed at 2 and 5 M HCl media, suggesting formation of similarly protonated species in the acid range examined.

Experimentally observed salt effect-data when plotted (Fig. 1) gives three linear curves for 1-3 μ studies, meeting on the Y-axis (Fig. 1), giving a constant contribution (2.0×10^{-2} min^{-1}) *via* the neutral species of the phosphorodiamidate. The trend of the slopes indicates a negative salt effect ($b'_{H^+} = -0.16$) on the acid-catalyzed rates. Using 2nd empirical term of the Debye-Hückel equation[9], eqn. 1 comprises of rates *via* both the reactive species, the neutral and the conjugate acid. Individually, the contribution of

$$Ke_{calcd.} = k_{H^+} C_{H^+} + k_N \text{ (fixed)} \quad (1)$$

the conjugate acid species is represented as eqn. 2

$$k_{H^+} C_{H^+} = k_{Ho^+} C_{H^+} e^{b_{H^+}} \mu \quad (2)$$

where, k_{H^+}, is the acid-catalyzed rate, $k_{H_o^+}$ is the acid-catalyzed rate at zero ionic strength, b_{H^+} is slope and k_N is the rate *via* the neutral species. The contribution made by the neutral form is observed to be constant and from eqn. 2 the calculated rates are derived after solving it logarithmically;

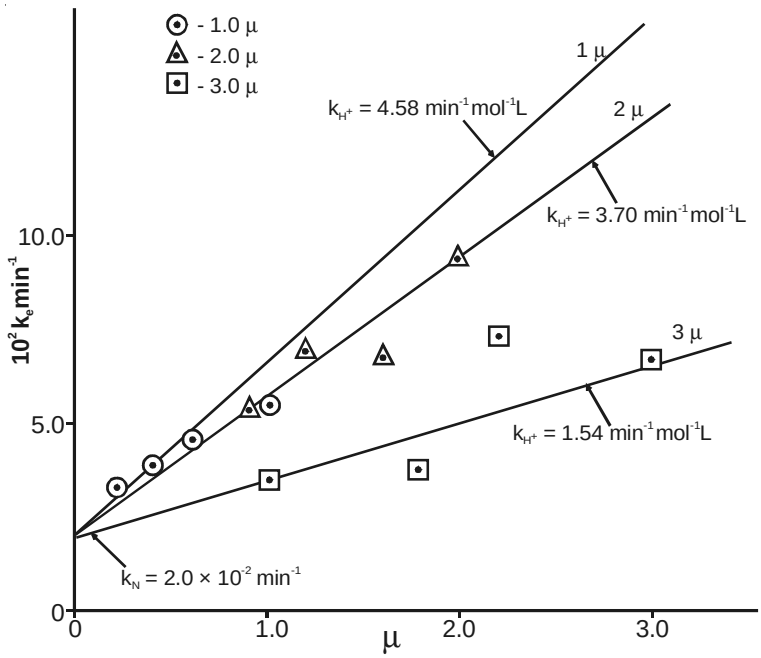


Fig. 1. Hydrolysis of Di-*o*-nitro-*p*-chloro-phenyl phosphoramidate maintaining constant ionicstrengths at 40 ± 5ºC

$$\log k_{H^+} C_{H^+} = \log k_{Ho^+} + \log C_{H^+} - b'_{H^+} \mu \quad (3)$$

The value is then added to k_N as required (Table-1) throughout the acid range examined. These rates are found to coincide (Table-1) with the observed rate coefficients. The salt effect data accounts for the presence and the contribution of neutral (I) and the conjugate acid (II) species

during acid hydrolysis. It also postulates specific acid catalysis for the present compound.

TABLE-1
KINETIC DATA FOR THE HYDROLYSIS OF *o*-NO_2-*p*-Cl PHENYLPHOSPHORIC DIAMIDE AT DIFFERENT ACID MOLARITIES AT 40 ± 0.5°C (12% DMSO: H_2O, v/v)

HCl (M)	$10^2\ {}^{a}k_{H^+}\ C_{H^+}$	$({}^{a}K_{H^+}\ C_{H^+} + {}^{b}k_N) = 10^2\ k_e$ (min^{-1}) (calcd.)	$10^2\ k_e$ (min^{-1}) (obsd.)[c]
0.1	0.64	2.64	2.49
0.5	2.74	4.74	4.07
1.0	4.57	6.57	5.47
2.0	6.32	8.32	9.39
3.0	6.56	8.56	6.66
4.0	6.05	8.05	10.31
5.0	5.23	7.23	14.51
6.0	4.34	6.34	6.31
7.0	3.51	5.51	5.30

a: $2 + \log k_{Ho^+} = 0.82$ (plot not included); $b'_{H^+} = -0.16$, b: $2.02 \times 10^{-2}\ min^{-1}$
c: k_e obsd. For the corresponding mono-*o*-NO_2-*p*-Cl phenylphosphoramidate[19] at 50°C in aq. medium = $1.22 \times 10^{-2}\ min^{-1}$

During the kinetic study, the role of one of the products, the parent amine itself was verified and the hydrolysis (0.5 M HCl) showed the rates to be nearly independent of the concentration of the amine formed, during the progress of acid hydrolysis.

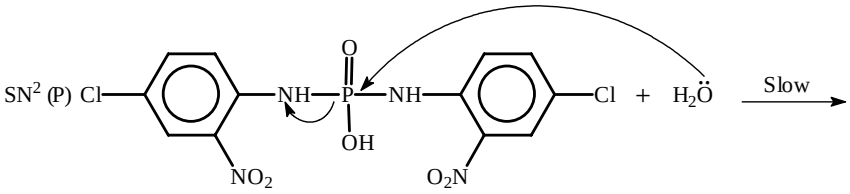
Temperature effect studies led to the Arrhenius[10] or thermodynamic parameters (Table-2) which lead the favouring the bimolecular mode of hydrolysis. Low positive entropy value suggests the formation of an activated complex and it is also compensated by high frequency factor, thereby resulting in fast acid hydrolysis, even at a little more than body temperature.

TABLE-2
ARRHENIUS PARAMETERS (AT 1.0 M HCl) FOR DISUBSTITUTED PHENYLPHOSPHORIC DIAMIDE

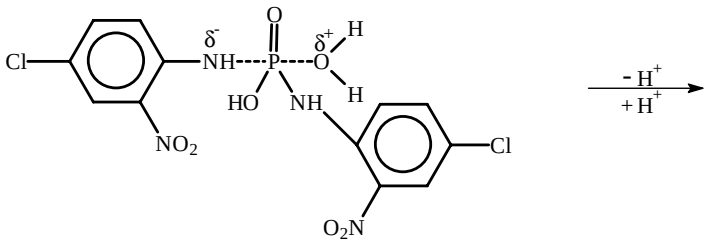
Energy of activation 'E'	Frequency factor (A)	Entropy of activation $\Delta S^{\neq}$	Enthalpy of activation $\Delta H^{\neq}$	Free energy $\Delta G^{\neq}$
16.41 K cals/mol or 68.59 KJ/mol	$9.45 \times 10^7\ sec^{-1}$	-0.0524 e.u.	15.79 K cals/mol or 66.00 KJ/mol	15.77 K cals/mol or 65.91 KJ/mol

Concentration effect studies at 2 M HCl indicate a little lowering in reaction rates with the rise in substrate concentration, but the overall rate is decided as pseudo-first order, due to excess of the medium used.

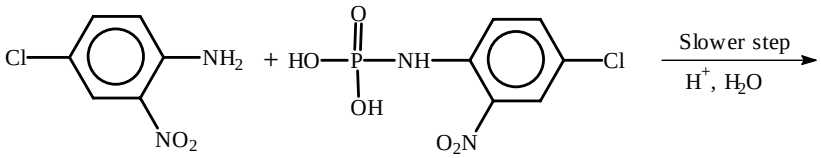
Concepts in higher acid media (data and Figs. not included) due to Hammett plot[11] (slope = 0.32); Zücker-Hammett plot[12] (0.625); Bunnett plots[13] (w = 9.00 and w* = 3.33) and Bunnett-Olsen plot[14] (ϕ = 1.55) all favour bimolecularity just like Arrhenius[10] parameters (Table-2). The value of ϕ also recommends protonation *via* the hydronium-ion species, in a fast pre-equilibrium proton-transfer step of the neutral species (I). No mechanism is available here to distinguish whether species (I) is undissociated or zwitter ionic in nature. Yates and McCleland[15] hydration parameter, γ, being 3.33 suggests the involvement of three water molecules during hydrolysis (**Scheme-I**).



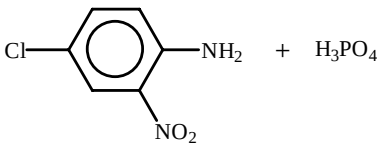
Neutral species (I)



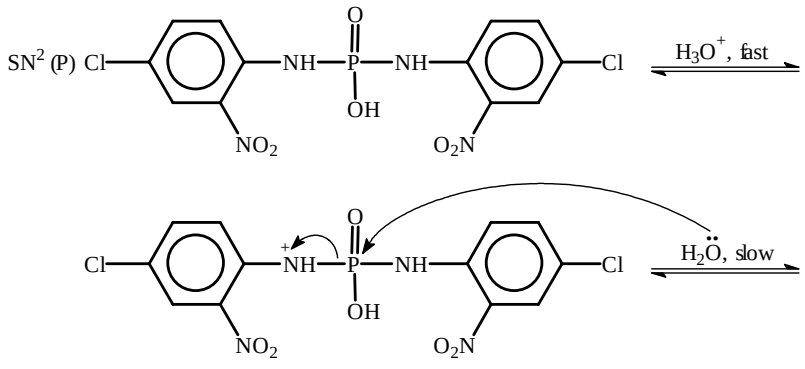
Transition state (with creation of charges)



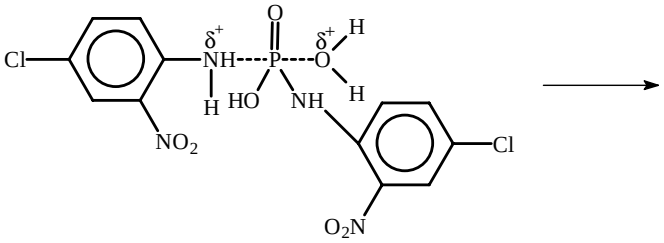
Corresponding Monoamidate



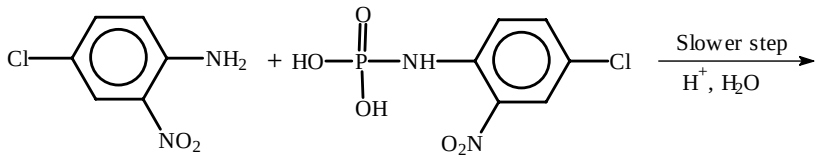
Scheme-I Bimolecular mechanism of hydrolysis *via* the neutral form of the diamidate in the entire acid region



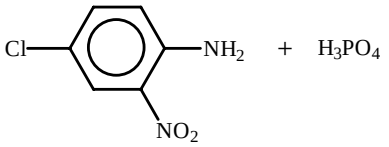
Conjugate acid species (II)



Transition state (with dispersal of charges)



Corresponding Monoamidate



Scheme-II Bimolecular route of hydrolysis of *o*-NO_2-*p*-Cl-phenyl phosphoramidate in the entire acid region

Solvent effect study shows around 11 times elevation in rates (10^2 k_e obsd. min^{-1}) from 0.18 to 2.02 with a change over from 18 to 100 % DMSO[16]. Again at 1 M HCl, the rates were nearly doubled only, when DMSO was increased upto 90 %. The study at 2 M HCl, shows the rate rise from 8.56 × 10^{-2} to 11.52 × 10^{-2} min^{-1} when 12 % DMSO is doubled. Such an aprotic solvent promotes hydrolysis mainly by acting as a good nucleophile.

Reagents with varying nucleophilic tendencies were used to examine there influence on the present phosphordiamidate and the following results are observed:

Acid/reagents	HCl	> NaCl	> NaF	> NaBr	> NaI
10^2 k_e (min^{-1})	4.76	3.14	3.02	2.63	2.18

Effect of Reagents (0.1 M) at 0.01 M HCl at 40 (± 0.5)°C

from these, it is decided that Cl^- and F^- are better nucleophiles than Br^- and I^-.

It needs to be mentioned here that the corresponding monoester has been investigated (as its barium salt) at 50 ± 0.5°C in an aqueous-acid medium. On this basis, the monoester is expected to hydrolyze rather slowly at 40 ± 0.5°C (*i.e.* the temperature used for the diamidate under observation), its intervention during acid hydrolysis is thereby decided.

During the progress of hydrolysis, the formation of the corresponding amine was checked qualitatively by an azo-dye test[17], postulating P-N bond fission of the diamidate.

o-NO_2-*p*-Cl-phenylphosphoric diamide was screened for its antimicrobial activity[18] and it has been found that the MIC values of this compound, for *Candida albicans* and *Cryptococcus* neoformans are 25 and 50 mg/mL, respectively. Such an activity is attributed to a combination of both -NO_2 and -Cl groups in the aryl matrices.

On the basis of all the above results, a bimolecular mode of hydrolysis is arrived at with P-N bond fission, *via* the two reactive forms, for the present *o*-NO_2-*p*-Cl-phenylphosphoric diamide (**Schemes I** and **II**). An important observation is that the corresponding monoester[19] in acid (Table-1) shows that the latter hydrolyses *ca*. twenty four times slower than the diamidate, an unusual aspect in the study of C-N-P containing compounds. This leads to an indirect conversion of the diamidate *i.e.*, *via* the corresponding monoamidate into H_3PO_4, one of the final products of hydrolysis.

REFERENCES

1. L.F. Audrieth and A.D.F. Toy, *J. Am. Chem. Soc.*, **64**, 1553 (1942).
2. A.D.F. Toy and K.L. Filers, Ger. Offen. 2,149,377, 13 April 1972.
3. A. Streitwiser and C.H. Heathcock, Introduction to Organic Chemistry, Collier MacMillan International, p. 1036 (1976).
4. P.I. Alimov, O.N. Fedorova and I.V. Cheplanova, *Izvest. Kazan. Filiala. Akad. Nauk. S.S.S.R., Ser. Khim. Nauk.*, **4**, 49 (1957).
5. W.P. Jencks, Catalysis in Chemistry and Enzymology, McGraw-Hill Book Co., New York, pp. 76-77, 148 (1969),
6. V.M. Clark, G.W. Kirby and A. Todd, *J. Chem. Soc.*, 1497 (1957).
7. R.J.L. Allen, *Biochem. J.*, **34**, 858 (1940).
8. E.M. Kosower, An Introduction to Physical Organic Chemistry, John Wiley & Sons, pp. 84, 343-351 (1968).

9. R.A. Robinson and R.H. Stokes, Electrolyte Solutions, Butterworth Scientific Publications, London, p. 559 (1959).
10. S. Arrhenius, *Z. Physik. Chem.*, **4**, 226 (1889); K.J. Laidler, Chemical Kinetics, Tata-McGraw Hill Co., New Delhi, edn. 2, p. 203 (1965).
11. L.P. Hammett and A.J. Deyrup, *J. Am. Chem. Soc.*, **54**, 2721 (1932).
12. L. Zücker and P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).
13. J.F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960).
14. J.F. Bunnett and F.P. Olsen, *Can. J. Chem.*, **44**, 1917 (1960).
15. K. Yates and R.A. McCleland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).
16. C. Kalidas and N. Chittanathan, *J. Indian Chem. Soc.*, **51**, 479 (1974).
17. A. Singh, Ph.D. Thesis, Jiwaji University, Gwalior, India (1995).
18. B.S. Furniss, A.J. Hannaford, T.W.G. Smith and A.R. Tatchell, in: A.I. Vogel's, A Practical Organic Chemistry, Addison-Wesley Longman Ltd., London, edn. 5, p. 1215 (1989).
19. B.D. Davies, R. Dublecco, H.N. Eisen and H.S. Ginsberg, Microbiology, Harper and Row Publishers, edn. 4, p. 751 (1990).
20. A.H. Zewail, Scientific American: Feature Article, The Noble Prizes of 1999, pp. 2-4 (2000).

(*Received*: 13 February 2006; *Accepted*: 27 December 2006) AJC-5305