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Kinetic Study of Hydrolysis of O-Methyl,N-2-Chloro,4-Nitro-Phenyl phosphoricamide in Buffer Media

Manzoor Ahmad Khanday and Shashi Prabha
School of Studies in Chemistry,
Jiwaji University, Gwalior, (Madhya Pradesh), INDIA

(Corresponding author: Manzoor Ahmad Khanday)

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ABSTRACT: The mixed diester, O-Methyl,N-2-Cl,4-NO_2-Phenyl phosphoric-amide, has been hydrolysed and kinetically investigated in the pH-range varying between 1.24 to 10.0 values at 98(±0.5)°C in AcOH –H_2O medium, involves a minimum at pH 4.17 and shows the presence of a Monoanion species only. The substrate concentration was maintained as 8.0×10^{-4}M. The calculation was made using second-order rate coefficients, and due to the presence of medium in excess, AcOH-H_2O or water, these rates are better called as pseudo-first-order rate coefficients. The mixed diester shows that a Neutral species also contributes in the pH range, 1.24-2.20 with a specific contribution of the Zwitterionic species at pH 1.24 only. P-N bond fission was inferred for the hydrolysis of the mixed diester under observation in the pH range.

I. INTRODUCTION

Organophosphoramidates display a great role in the biological [1], industrial [2], agricultural [3] and medicinal [4] fields. Apart from the importance of phosphate compounds, nitro compounds too have a very significant or key role because of their powerful antibiotic and other pharmacological activities. The common broad spectrum antibiotic, chloramphenicol, was the first natural product recognized to possess an aromatic nitro group, and is used for the treatment of typhoid, bacterial meningitis as well as other pencillin resistant staphylococcal infections. Another NO_2-group containing compound, 2-nitro imidazole (Azomicin) has low toxicity and possesses a broad spectrum activity against both bacteria and protozoa. Many organophosphorus compounds are commonly used as insecticides though being extremely toxic to humans [5-6]. Such compounds are also utilized as flame retardants [7], plasticizers [8]. The two nucleoside analogues, 3-azidotoxithymidic(AZT) and 2,3-dideoxycytidin-(DDC) have been the rapaeutically used for the treatment of acquired immune deficiency syndrome(AIDS) patients [9]. Due to the significance of some of the features related to the presence of the NO_2 group, the present study of O-methyl, N-2-Cl, 4-No_2-Phenylphosphoric amide, which has been synthesized in our laboratory has been undertaken. This compound was also expected to exhibit some characteristic behavior of physiological utility. In general majority of the organophosphorous compounds (C-N-P or C-O-P or C-S-P) have biochemical importance because of the role of the orthophosphates (C-O-P) especially as acetylcholinesterase inhibitors or even worse.

II. EXPERIMENTAL

The synthesis of the mixed diester, O-Methyl,N-2-Cl,4-NO_2-Phenyl phosphoricamide, was accomplished by a two step process, involving first the phosphorylation of methanol to form methoxyphosphorodichloridate; and its treatment with 2-Cl,4-NO_2-aniline in the second step to form the desired product. Hydrolytic kinetic study has been carried out at $98(\pm)^{\circ}$C by using 8.0×10^{-4} M concentration of the diester solution. The hydrolysis product, phosphoric acid in the form of inorganic phosphate, was estimated with the help of UV/VIS spectrophotometry using Allen's [10] Modified Method. The buffer solutions were prepared [11] using appropriate mixture of KCl, HCl, KHP, NaOH, borax, $NaHCO_3$ & H_3BO_3.

III. RESULTS AND DISCUSSION

Hydrolytic kinetic study of O-Methyl, N-2-Cl, 4-NO_2-Phenylphosphoric amide has been carried out at $98(\pm)^{\circ}$C in the pH range from 1.24 to 10.0 by using appropriate buffers.

Fig.1 shows the pH-log rate profile of the study. From the pH log-rate profile, it is seen that some rate maxima occur at pH 3.33, pH 5.10, pH 10.0 mainly.

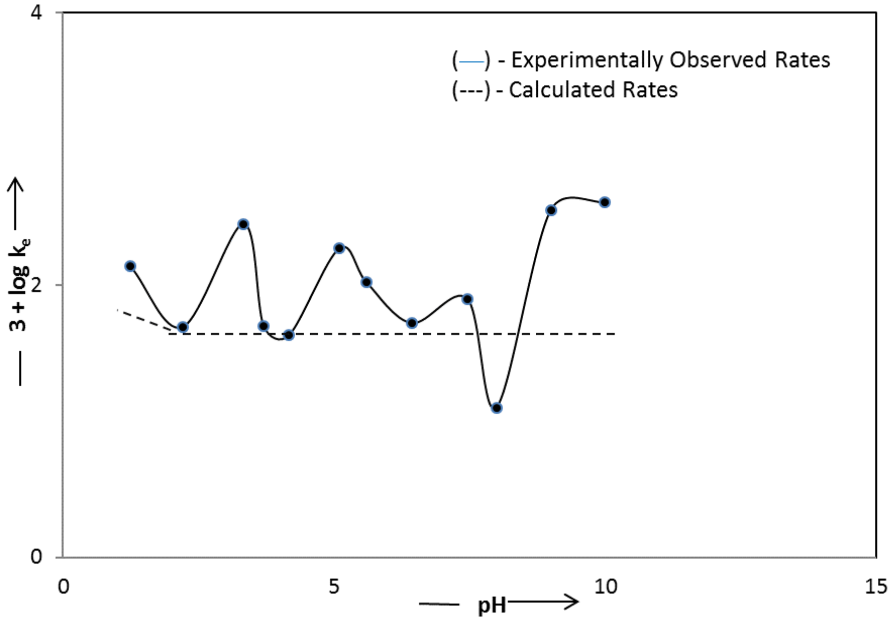


Fig. 1. pH–Log Rate Profile of O-Methyl, N-2-Cl, 4-NO_2-Phenylphosphoric amide.

However, the minimum rates observed at pH 4.17 are of classical nature, strongly supporting the nature of the compound as being equivalent to a diester of the common type. During hydrolysis in the pH-range, we have:

$$k_e = k_N + k_M \quad \ldots(i)$$

Also, $$k_M = k_{M0} \cdot M/N+M \quad \ldots(ii)$$

and,

$$k_N = k_{NO} \cdot M/N+M \quad \ldots(iii)$$

where, k_M and k_N represent rates via the Monoanion and the Neutral species respectively; and k_{MO} corresponds to the rates via the minimum rates at pH 4.17 chosen in the pH-range; and also k_{NO} corresponds to the rates via the maximum Neutral form at the lowest value of pH in particular.

The calculated rate-coefficients are based on equations (ii) and (iii), and the fractions (N/N+M), (M/N+M) for the Neutral and the Monoanion forms respectively are determined. For this, the rates observed at pH 4.17 are taken to correspond to k_M and are further equal to k_{M0} and are shown as below:

$$k_M = k_{M0} = 4.31 \times 10^{-2} M^{-1} min^{-1}$$

Table 1: Observed Rate Data during the Hydrolysis of O-Methyl,N-2-Cl,4-NO_2-Phenyl phosphoricamide in the pH-Region in 12% AcOH-H_2O Mixture at 98±(0.5)°C.

S. No.	pH	$10^2 k_e$ ($M^{-1} min^{-1}$)	3 + log k_e
1	1.24	13.98[a]	2.14
2	2.20	4.96[b]	1.69
3	3.33	28.11[c]	2.45
4	3.70	4.90[c]	1.70
5	4.17	4.31[c]	1.63
6	5.10	18.53[d]	2.27
7	5.60	10.56[e]	2.02
8	6.43	5.21[e]	1.72
9	7.46	7.88[e]	1.90
10	8.0	1.24[e]	1.10
11	9.0	35.27[e]	2.55
12	10.0[f]	40.41[e]	2.61
13	12%AcOH-H_2O	2.29	2.36

Note: a - 25%AcOH-H_2O; b-20% AcOH-H_2O; c - wt. of cpd.=0.0031g (10.0 × 10^{-4}M) & 12%AcOH-H_2O Mixture, d - 2%DMF; e - without AcOH or DMF medium. f – pH measured and confirmed as 10.0 only.

In the low pH range during hydrolysis, the compound dissociates as:

$$N \leftrightarrows M + H^+ \qquad \ldots(v)$$

Therefore, $K = [M] \times [H^+]/[N]$

By transferring H^+ and by mathematical changes, we have:

$K/K + H^+ = M/N + M$

Similarly, $N/N + M = 1-(M/N + M)$

Therefore, from equation (vii), fractions of the Monoanion species may be calculated at different pH-values, taking into consideration the corresponding values of H^+ -ions for every pH……(vii) Also the fractions of the Neutral species of the mixed diester are decided on the basis of equation (viii). All these values for the fractions, the calculated and……(viii) the observed rate-coefficients are included in Table 2 given as below:

Table 2: Observed and Calculated Rate Coefficients for the Hydrolysis of O-Methyl, N-2-Cl, 4-NO_2- Phenyl phosphoric amide in the pH region (1.24-10.0) at 98±(0.5)°C.

S. No.	pH	N/N+M	k_N	M/N+M	k_M	10^2k_e(calcd.) ($M^{-1}min^{-1}$)	10^2k_e (obsd.) ($M^{-1}min^{-1}$)
1	1.24	0.460	6.43	0.540	2.33	8.76	13.98
2	2.20	0.085	1.19	0.915	3.94	5.13	4.96
3	3.33	0.007	-	0.993	4.27	4.27	28.11
4	3.70	0.003	-	0.997	4.30	4.30	4.90
5	4.17	-	-	0.999	4.30	4.30	4.31
6	5.10	-	-	0.999	4.30	4.30	18.53
7	5.60	-	-	0.999	4.30	4.30	10.56
8	6.43	-	-	0.999	4.30	4.30	5.12
9	7.46	-	-	0.999	4.30	4.30	7.88
10	8.00	-	-	0.999	4.30	4.30	7.73
11	9.00	-	-	0.999	4.30	4.30	35.27
12	10.0	-	-	1.000	4.30	4.30	40.41

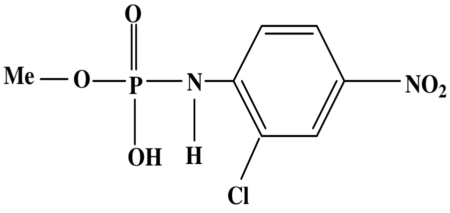
At the lowest pH 1.24, the observed rate coefficients are high in magnitude and most probably suggesting the presence and contribution of the Zwitterionic species However, at pH 2.20, the rates are lowered, which again rise at pH 3.33, leading to the participation of either the Neutral form (I) or the Mono anion species (VI) of the mixed diesters. However, a decision regarding this may be made from the dissociation constant (pK) of the compound under observation. During the entire pH study, the maximum rate coefficients have been observed at pH 5.10, while the minimum rates have been obtained at pH4.17. The latter, pH 4.17, has been considered to correspond to the presence of nearly 99.99% of the Monoanion species, but gives the least reactivity in diesters in general, and the same has been observed in case of mixed diester in question, as well. At this pH, the value of pK is determined as being equal to 1.17 only. This presumption for the Monoanion form (VI) has been employed for calculating the fractions of the species i.e., the Neutral as well as the Monoanion type. Table 1 compiles the rate data observed experimentally in the entire pH region for the mixed diester I, and Fig. 1 corresponds to the pH log-rate profile.

The calculated rates via the Monoanion and the Neutral species are determined with the help of equations (ii) and (iii) given earlier.

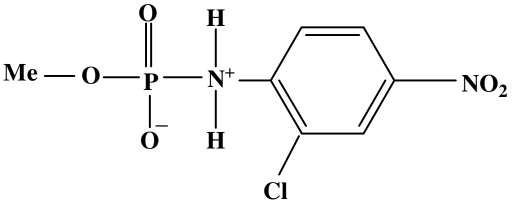
From Table 2, it is observed that the Neutral species is shown to be present between pH 1.24 to 3.70 and it decreases from 46% to 0.3% with the rise in pH, but has been shown to make no contribution towards the calculated rate coefficients except at pHs 1.24 and 2.20. In spite of this, it is unable to account and resemble the observed rate coefficients along with the rates via the Monoanion species at pH 1.24 only. At pH 2.20, both the Neutral and the Monoanion forms contribute and here the calculated rates agree with the observed rate coefficients as well. At and beyond pH 3.33 up to pH 10.0, it was possible to estimate the rates via the Monoanion species only. These calculated rates (k_M) have been included along with the Neutral rates (k_N) in Table 2 included earlier.

The rates via both the Neutral and the Monoanion (or Mono negative) species, however, do not agree with the rates observed at pH 3.33, because of the appearance of a rate maximum at this pH. The similarity between the two types of rates, the calculated and the observed rates, is seen at pH 3.70 followed by pH 4.17, where a typical rate minimum is observed. It is observed that only the Monoanion form, shown below operates also between pH 5.10 and pH 5.60 only, as the observed rates are higher in magnitude.

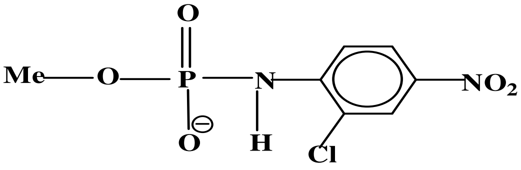
Again at pH 9.0 and pH 10.0, the rates deter-mined experimentally are nearly five times higher than those observed at pH 8.0, clearly showing that these rates might have been either due to a change in mechanism from S_N2 (P) to S_E2 (P) or a special of behaviour of the compound is shown at these alkaline pH-values. The high magnitude of rates favours the first reasoning change of mechanism to S_E2 (P) type of mechanism.



(I)-Neutral Species



(II)-Zwitterionic Species



(VI)-Monoanion Form

During the pH-study as above, it has also been noticed that the two rate maxima appear at pH 5.33 and 5.10. Somewhat higher rates are also observed at pH 5.60. These rate maxima may arise due to the liberation of 2-Cl,4-NO_2-Penyl phosphate or Monomethyl phosphate, during the progress of hydrolysis under the typical pH-values, at which their corresponding Monoanions might have been formed. The presence of acetic acid has already been shown not to affect the pH-values due to its role as a solvent only.

Type of Bond Fission Undergoing Cleavage during Hydrolysis in the pH-Region:-

During the kinetic study, it was possible that the compound exhibits fission of some kind, either P-N or C-N mainly. Since, by P-N fission, the parent amine, 2-Cl, 4-NO_2-amiline may be liberated as one of the end products in the earlier pH runs (pH 1.24-3.70), it was checked for its formation only qualitatively. Thus, an azo-dye test was conducted, which indicated the formation of the parent amine, due to the orange-red dye that was precipitated during the test. The rupture of C-N bond was not expected, because that may lead to an unstable aryl system only. Such a kind of bond fission is also decided by the help of some comparative kinetic data of the phosphorodiamidates along with some other mixed diesters.

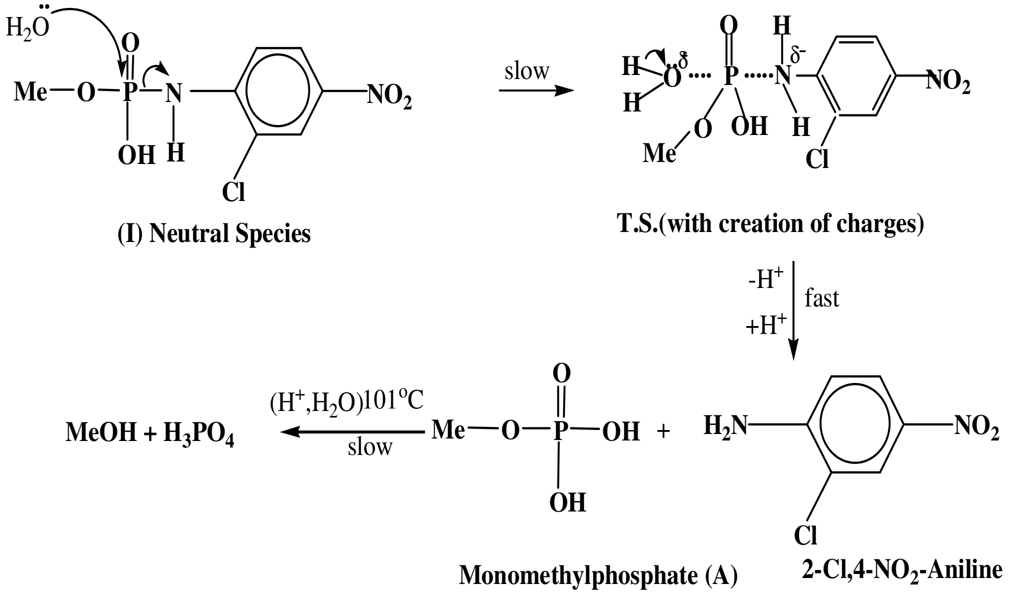
Table 3: Comparative Kinetic and Thermodynamic Data for the Hydrolysis of Some Phosphoric amides and Diamidates/Diamides in pH-Region showing Bond Fission.

S. No	C-N-P Ester(Di)	Temp (±0.5)°C	Minimum pH	$10^2 k_e$ ($M^{-1} min^{-1}$)	ΔE $KJmol^{-1}$	$\Delta S^{\ddagger}$ e.u.	Bi/P-N	Ref.
1.	o,p-Di-Cl- (C-N-P)	50	2.20	16.2 min^{-1}	104.8	+2.14	Bi/P-N	12
2.	o,p-Di-Cl-NO_2 (two C-N-P)	98	4.17	0.04 min^{-1}	45.93	-59.57	Bi/P-N	13
3.	O-NO_2-p-Meo- (two C-N-P)	98	4.17	2.2 min^{-1}	43.84	-54.42	Bi/P-N	14
4.	O-NO_2-p-l- (C-N-P)	40	3.70	0.032 $M^{-1}min^{-1}$	32.85	-6.20	Bi/P-N	10
5.	o,p-Di-MeO- (two C-N-P)	40	3.70	0.24 $M^{-1}min^{-1}$	49.53	-19.80	Bi/P-N	15
6.	O-Methyl,N-o-Me, m-NO_2-Phenyl phosphoricamide (C-O-P&C-NP)	98	5.10	116.6 $M^{-1}min^{-1}$	100.83	+9.95	Bi/P-N	16
7.	O-Methyl,N-2-Cl,4-NO_2-Phenylphosphoricamide	98	4.17	43.1 $M^{-1}min^{-1}$	36.90	-42.92	Bi/P-N	This work

The rate data via the Monoanion form has been complied and presented in Table 3. It may be noticed from Table 3 that the $\Delta E^{\ddagger}$ values are much nearer in magnitude except for the first member, *i.e.* o,p-Di-Cl-Phenyl phosphoro-diamidate [12]. For the latter, the value of entropy ($\Delta S^{\ddagger}$) is both low as well as +ve, while the other members included in the Table 3 show almost similar, and –ve values, so that the forward reaction during the hydrolysis is greatly promoted. All these features support the bimolecular nature and P-N bond fission for the hydrolysis of the mixed diester under observation in the pH range. As the Neutral, the Zwitterionic and the Monoanion species operate in the specific region of the pH range examined. On this basis, the following three reaction routes for their reactive forms are being represented as below:

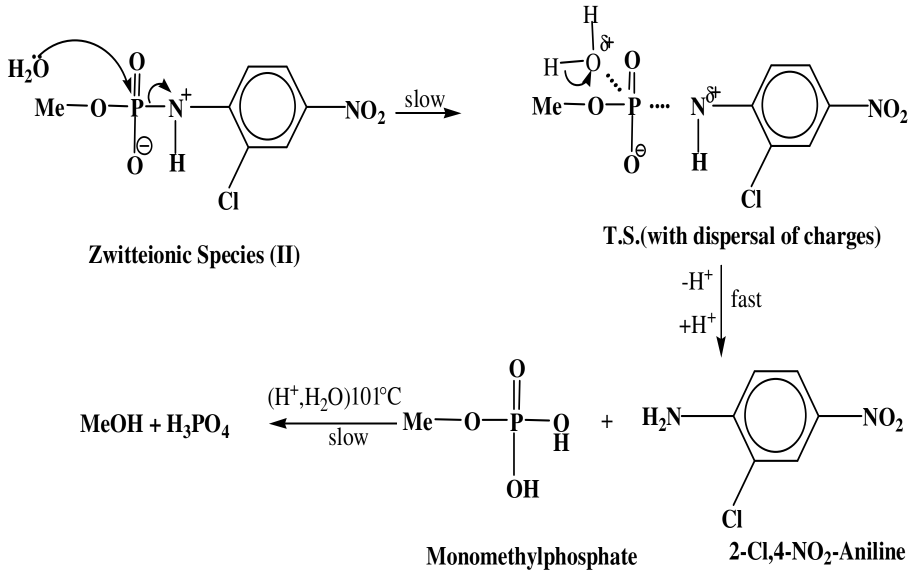
Mechanisms of Hydrolysis under pH-Controlled Conditions in 12% AcOH-H_2O Mixture at 98 (±0.5)°C:

(i) S_N2 (P): Bimolecular Hydrolysis via the Neutral (I) form of the Mixed diester I at low pH – conditions (pH 1.24 – pH 2.20):

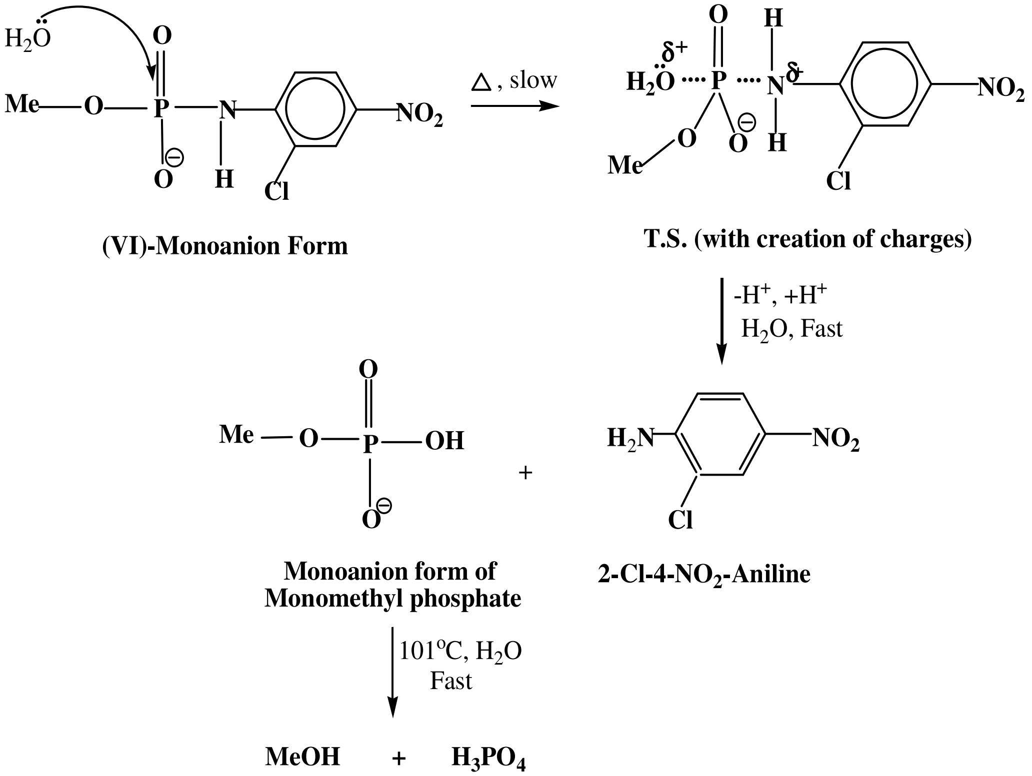


(ii)

S_N2 (P): Bimolecular Hydrolysis via the Zwitterionic species (II) at pH 1.24 only:



(iii) S_N2 (P): Bimolecular Hydrolysis via the Monoanionic Form(VI) at pH 1.24 only:



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