Asian Journal of Chemistry Vol. 8, No. 1 (1996), 129–133

Hydrolytic Dephosphorylation of an Aryl Phosphoramidate

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Mono-2-NO_2-4-Cl phenyl phosphoramidate has been kinetically pursued for its hydrolysis at 50 ± 5°C and Allen's modified method has been employed for quantitative results. First order rate coefficients have been calculated in the entire acid range, 0.01–7.0 M HCl ionic strength studies lead to the fixed contribution of the undissociated form between 0.5–3.0 M, while the monoprotonated form solely contributed in the higher acid media, 4.0–7.0 M HCl. Beyond 4.0 M, water activity governs the rate of hydrolysis and a maximum number of three water molecules, derived from both Yates and McCleland correlation as well as Bronsted-Bjerrum equation, have been arrived at to transform the ester into its transition state. Solvent effect, concentration and Arrhenius parameters have been used to confirm the above results.

INTRODUCTION

Synthesis and study of an aryl phosphoramidate has been undertaken with a view to examining the reactivity due to the presence of strongly electron withdrawing substituents in the aryl matrix. The synthesis of the specific monoamidate has been achieved and for this the application of the newer range of catalysts, the micelle, was the main constituent of the reaction mixture. Thus, both synthesis and kinetic study have been made with these aspects in mind.

EXPERIMENTAL

The monoester of 2-nitro-4-chloro phenyl phosphoramidate with C—N—P linkage has been synthesized by employing the new catalyst, the surfactant. Its hydrolytic fragmentation has been studied in the acid-range at 50 ± 0.5°C, using Allen's modified method[1], in the aqueous medium.

RESULTS AND DISCUSSION

Studies have been conducted at varied neutral electrolyte concentrations and first order rate coefficients determined. Using the data a plot was drawn, which shows a fixed contribution of the undissociated form of the monoester. However, there is a regular increase in the value of acid catalysed rates, with the rise in acid molarity, keeping the total ionic strength constant. It also involves the modified neutral form as the third reactive form, although at low acid molarity only.

The rising slopes of the linear curves indicate positive ionic strength effect leading to the contribution of the conjugate acid species of the present monoamidate. These linear curves are based on the 2nd empirical term^2 of Debye-Hückel equation.

$$k = k_0 \exp b\mu \tag{1}$$

In the present case, above equation can be modified as

$$k_N = k_{N_0} = 4.3 \times 10^{-3}\ \text{min}^{-1} \tag{2}$$

The equation (1) can also be modified for the conjugate acid form of this ester as

$$k_H = k_{H_0^+} \exp b_{H^+}\mu \tag{3}$$

Table-1 shows that the neutral (alongwith zwitter ionic) form operates between 0.1 to 3.0 M HCl. After this, contribution of conjugate acid species may be evident in the acid range 4.5 to 7.0. This exhibits the maximum rate at 4.0 M HCl, showing the moderate basic nature of monoamidate.

TABLE-1
CALCULATED AND OBSERVED RATE DATA FOR THE HYDROLYSIS OF MONO-2-NO_2-4-Cl PHENYL PHOSPHORAMIDATE AT 50 ± 0.5°C

S. No.	HCl (M)	$10^3\ k_N$ min^{-1}	$10^3\ k_{H^+}C_{H^+}$ min^{-1}	$10^3\ k_e$ (calcd.) min^{-1}	10^3 (obsd.) min^{-1}
1.	0.1	4.3	—	4.30	3.63
2.	0.5	4.3	—	4.30	4.35
3.	1.0	4.3	—	4.30	5.30
4.	2.0	4.3	—	4.30	5.26
5.	3.0	4.3	—	4.30	4.74
6.	4.0	—	17.29	17.29	15.86
7.	4.5	—	21.09	15.63^a	13.87
8.	5.0	—	25.35	12.42^a	12.18
9.	6.0	—	35.64	9.59^b	11.80
10.	7.0	—	48.75	7.09^c	9.79

For a, b, c, n is 1, 2 and 3 respectively.

In higher acid range, the involvement of water activity becomes significant; thus in this region Eq. (3) can be modified as

$$k_e = k_{H_0^+}C_{H^+} \exp b_{H^+}\mu a(H_2O)_n \tag{4}$$

In concentrated acid media, *i.e.* > 4 M, the mono-protonated species solely contributed towards the total calculated rates. Use of specific concepts like the Hammett correlation (slope 0.31) indicates the involvement of water molecule in the r/d stage of hydrolytic degradation. Bimolecular nature of reaction is further supported by Zücker-Hammett[4] plot (slope 1.38). Two additional Bunnett[5] paramters, w and w* corresponding to 8.57 and 2.07, also support the above type of mechanism with the formation of a transition state during hydrolysis. Yates and McCleland[6] correlation comprising of Hammett value (m = 0.24) and based on the activity of water, corresponds to a slope 3.33 suggesting the actual number of water molecules involved during hydrolysis. The similarity in value of γ (3.33) with that of no. of water activity used (n = 1, 2, 3) in the calculation of rates, it is suggested that the correlation is valid for the present member.

Further kinetic studies were conducted at three different temperatures and the various thermodynamic parameters[7] have been estimated and presented in Table-2. The values of E at both the acid molarities (1.0 M and 4.5 M) clearly and strongly favour the requirement of second reactant for both the undissociated and the monoprotonated species, operating at lower and higher acid media respectively. The E-based entropy of activation with negative values also suggests the formation of expanded transition states with water for both the reactive forms. The higher magnitude of A at both the acid molarities can again be assigned to the interaction of the solvent with the reactant in the suitable reactive state during bimolecular hydrolysis.

TABLE-2
ARRHENIUS PARAMETERS

HCl (M)	E. kJ mol^{-1}	A sec^{-1}	$\Delta S^{\neq}$ e.u.	$\Delta G^{\neq}$ kJ mol^{-1}
1.0	63.64	14.68×10^6	–31.89	25.50
4.5	73.44	13.67×10^8	–27.31	26.36

On changing to 10% AcOH-water medium from aqueous medium (5.30×10^{-3} min^{-1}) lowering in rates (4.26×10^{-3} min^{-1}) is observed indicating the absence of proton transfer. In higher percentage of AcOH (20%) the rates are elevated (8.30×10^{-3} min^{-1}), which has been assigned to a lowering of dielectric constant, thereby favouring protonation[8] and affecting the rate of hydrolysis by stabilising the transition state more than the reactant itself. Study on changes in concentration of substrate shows that the hydrolytic reaction corresponds to pseudo-first order type.

A comparison with other monoamidate was made, which suggests the P—N bond rupture of this monoester too. Due to the presence of phosphorus, the nucleophile is prone to attack at this position, leading to P—N bond fission. The product identification studies, when performed, indicate the liberation of free aryl amine during the hydrolytic dissociation, supporting the P—N bond cleavage of the present monoester.

The present monoamidate has been examined in the light of Hammett substituent correlation[3] in combination with Taft[9] values and a plot was drawn between log rate and σ or $\sigma + \sigma^*$ giving a slope ($\rho = -1.16$) (Table-3) justifying the common type of behaviour of the diverse members included, thereby favouring P—N bond cleavage.

TABLE-3
HAMMETT AND TAFT SUBSTITUENT CONSTANTS DATA FOR HYDROLYSIS OF SOME ARYL PHOSPHORAMIDATE

S. No	Monophosphoramidate	Temp. (°C)	10^3 k_e (obsd.) min^{-1}	σ $\sigma + \sigma^*$	Ref.
1.	P—Cl aniline	20	1.50	+0.23	10
2.	2-NO_2-4-MeO aniline	60	48.69	+0.53	11
3.	2-NO_2-4-Cl aniline	50	15.86	+1.03	This work

On the basis of the different experimental results and the discussion thereof, the hydrolysis of the monoamidate has been postulated to proceed *via.* the following three reactive forms at different acid molarities.

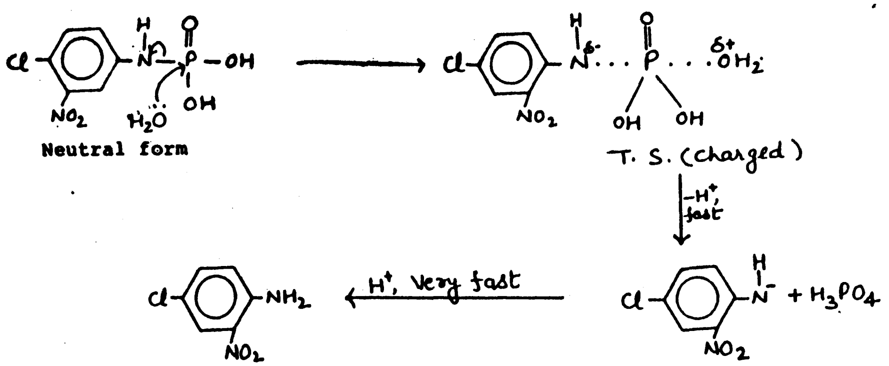

Chart-1 $S_N2(P)$ Mechanism for the hydrolysis of the neutral form.

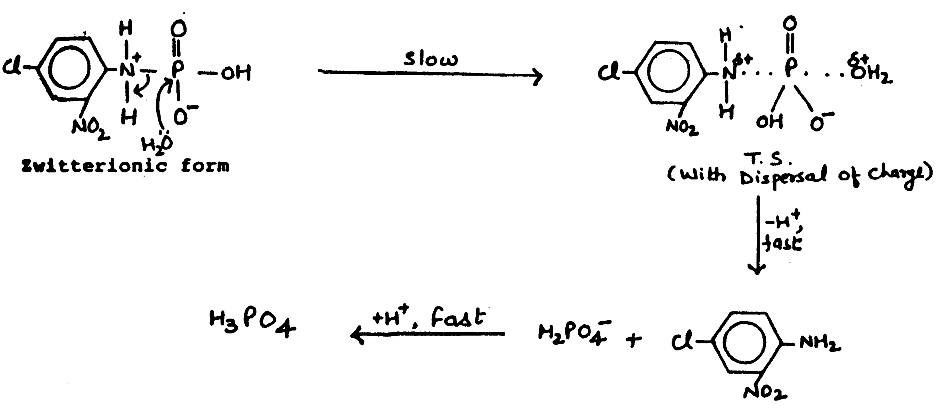

Chart-2 $S_N2(P)$ Mechanism for the hydrolysis of the zwitter ionic form.

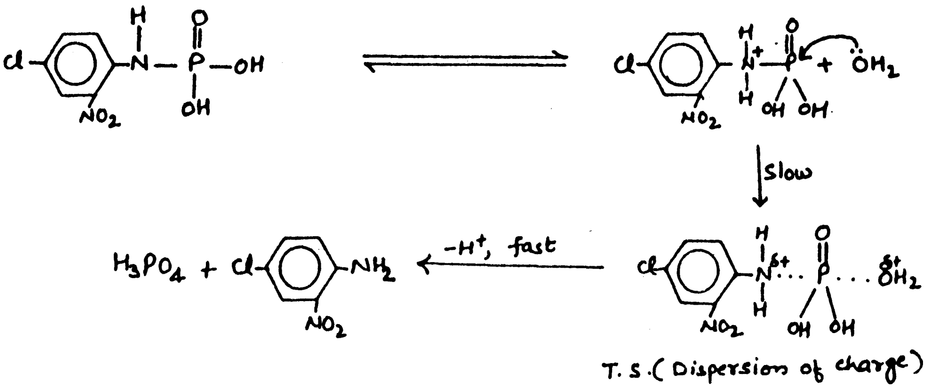

Chart-3 $S_N2(P)$ Mechanism for the hydrolysis of the monoprotonated form.

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(*Received*: 26 May 1995; *Accepted:* 26 August 1995) AJC-1003