Asian Journal of Chemistry Vol. 15, No. 1 (2003), 217–224

Micellar Synthesis and Acid Hydrolysis of a Phosphoric Diamide

ANURADHA KHANWALKAR and SHASHI PRABHA*
School of Studies in Chemistry, Jiwaji University, Gwalior-474 011, India

Phosphoric bis-(2,4-dimethoxyphenyl amide) chloride, a C—N—P containing bis-amide, has been kinetically examined (a rate maximum at 4.0 M) during hydrolysis in 0.01–7.0 M HCl at 40 ± 0.5°C. Zwitter ionic-neutral (or protonated-neutral) and conjugate acid species have been assessed as the major reactive forms, undergoing bimolecular hydrolysis with P—N bond fission. Arrhenius parameters and other concepts support bimolecular mode with 3–4 water molecules involved in the transfer of proton, formation of transition state and overall hydrolysis. Out of 20, only 3 reaction routes operate during hydrolysis. Synthesis has been performed using both parent amine as well as $POCl_3$ in the presence of meagre amount of CTAB.

Key Words: Phosphoric amide, Synthesis, Micelles, Hydrolysis.

INTRODUCTION

Many of the organic phosphoric aryl amides have been found promising as both, synthetic[1] as well as biological molecules, *e.g.*, as anti-HIV[2] compounds, metabolic intermediates[3], antitumours[4] and insecticides. These phosphoric arylamides (containing C—N—P linkage/s in them) are safer than their corresponding C—O—P derivatives largely, and, therefore, find much use in industry.

Looking to the multifarious applications[1–5] as above, phosphoric bis-(2,4-dimethoxyphenyl amide) chloride has been synthesised and its kinetic investigations carried out during hydrolysis mainly in the acid medium (0.01–7.0 M HCl) at 40 ± 0.5°C. Initially, the instability cum reactivity of the ester solely in the aq. medium was ascertained (2.5×10^{-3} L mol^{-1} min^{-1}) under similar temperature conditions. Effects of kinetic variables like neutral electrolyte and temperature etc. were carried out to examine and interpret its behaviour under a variety of conditions, near body temperature.

EXPERIMENTAL

A facile synthesis of phosphoric bis-(2,4-dimethoxyphenyl amide) chloride was achieved by stirring (*ca.* 5.5 h) the corresponding parent amine and $POCl_3$ (1 : 1) in the presence of CTAB (0.01 g) in dry benzene at room temperature (32 ± 1°C), and gave a purple-coloured solid, m.p. 210–212°C. Recrystallisation was done with $CHCl_3$ giving a $CHCl_3$-insoluble product with m.p. 212–214°C.

Concentration of the diamide was maintained as 8.0×10^{-4} M in all the runs except the concentration effect runs.

Estimation of P during hydrolysis in the entire acid region was done by Allen's modified method. IR also shows the typical P═O and C—N—P peaks at *ca.* 1219 cm^{-1} and 1100–800 cm^{-1} respectively.

All the reagents used were of A.R. (Qualigens) grade.

RESULTS AND DISCUSSION

Phosphoric bis-(2,4-dimethoxyphenyl amide) chloride thus synthesized has been kinetically studied during hydrolysis in 0.01–7.0 M HCl at 40 ± 0.5°C in an aq. medium. On hydrolysis, this C—N—P diester liberates parent amine, inorganic phosphate, etc., the latter being estimated quantitatively by Allen's modified method[6], with the help of Spectronics-20 spectrophotometer. The rate data is presented in Table-1 in the acid range.

The trend of the rates for neutral electrolyte effect studies (Fig. 1) although irregular with varying μ values (1.0–3.0), however, indicates a positive salt effect. Since all the three lines meet at zero value on the y-axis (Fig. 1), absence of any contribution by neutral form of the diamide is thereby decided for higher acid media in particular. On the other hand, the presence and contribution of the sole conjugate acid species is postulated on the basis of Fig. 1. For higher acid media, using the second empirical term of Debye-Hückel[7] equation, the rates are expressed as:

$$k_e = k_0 \cdot e^{b\mu} \tag{1}$$

where, k_e, k_0, b and μ are the observed rate coefficient, specific rate constant at zero value of the ionic strength, a constant and the ionic strength respectively. Also,

$$k_e = k_H^+ C_H^+ + k_N \tag{2}$$

Fig. 1 shows absence of contribution by the neutral species. eq. (ii) is reduced to the following:

$$k_e = k_H^+ \cdot C_H^+ \tag{3}$$

and

$$k_e = K_{H_0}^+ \cdot C_H^+ \cdot e b'_{H^+} \mu \tag{4}$$

$$\log k_e \text{ (calcd.)} = \log k_{H_0}^+ + \log C_H^+ + b'_{H^+} \mu \qquad \ldots (5)$$

where, k_H^+, $k_{H_0}^+$, C_H^+ and $b'_{H^+} \mu$ are the acid-catalysed rate at an ionic strength, acid-catalysed rate at zero ionic strength, concentration of hydrogen ions and a constant respectively. On the basis of eq. (5), another figure (not shown) was made, and from this $(1 + \log k_{H_0}^+)$ has been observed to be 0.80, while, b'_{H^+} is equal to –0.10. The rates were then calculated using eq. (5), on the basis of conjugate acid species of the diamide and theseare totally different in the low acid range (Table-1).

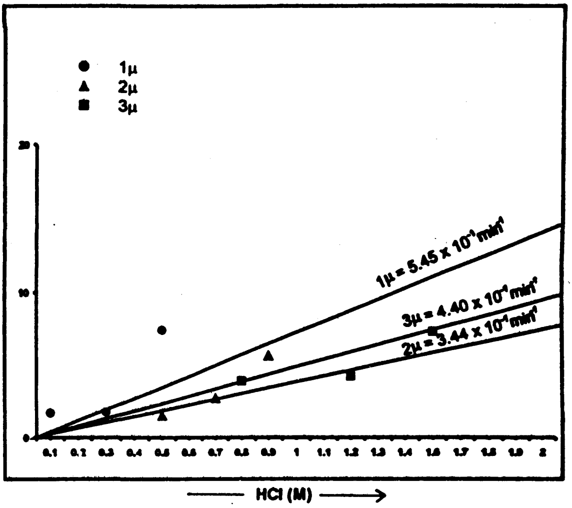


Fig. 1. Hydrolysis of Phosphoric bis-(2,4-dimethoxyphenylamide) Chloride at Constant Ionic Strengths at 40 ±0.5°C.

TABLE-1

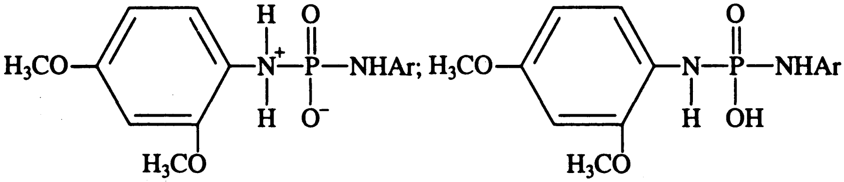
OBSERVED AND CALCULATED RATE-COEFFICIENTS FOR THE HYDROLYSIS OF PHOSPHORIC BIS-(2,4-DIMETHOXY-PHENYL AMIDE) CHLORIDE AT 40 ± 0.5°C

S.No.	HCl (M)	$k_N = k_e$ (obsd.) at pH 1.24	k_e (calcd.) L mol^{-1} min^{-1}	k_e (obsd.) L mol^{-1} min^{-1}
1.	0.00	–	–	0.0025*
2.	0.01	–	–	0.05
3.	0.10	0.22	0.22	0.17
4.	0.50	0.22	0.22	0.20
5.	1.00	0.22	0.22	0.21
6.	2.00	0.22	0.22	0.36
7.	3.00	0.22	0.22	0.23
		$K_{H^+}C_{H^+}$ L mol^{-1} min^{-1}		
8.	4.00	1.00	1.00	1.06
9.	5.00	0.99	0.29[a]	0.25
10.	6.00	0.95	0.28[b]	0.23
11.	7.00	0.88	0.24[c]	0.22

Note: (i) Values of n in eq. (6) for a, b, c are 3, 5, 2.5 and 2.0 respectively.

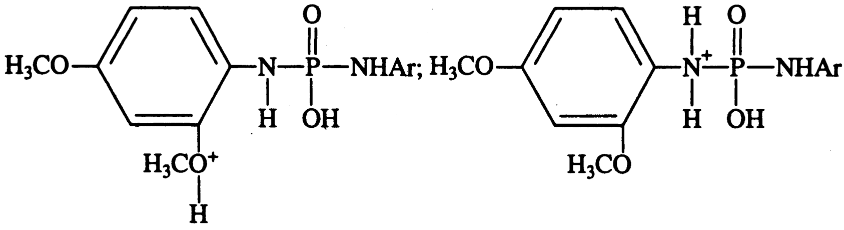
(ii) ≠ k_e for the corresponding monoamide is *ca.* 17,000 times faster in the similar aqueous medium only.

Table-1 shows that the lowest rates are observed at 0.01 M HCl, being attributed to the presence of the modified-neutral (or the zwitter ionic species (I)). However, between 0.1–3.0 M HCl, the rates are almost constant, but much higher (*ca.* 4–5 times) than those observed at 0.01 M HCl. Although the salt effect studies indicate the absence of neutral form, the magnitude of rates between 0.1–3.0 M HCl had to be decided indirectly, *i.e.*, from k_e (obsd.) at pH 1.24, which can only be derived due to the contribution made by the neutral species alone. Salt effect studies do not lead to the participation of the conjugate acid species in this acid range. The values are thus found to correspond to some other species, the neutral (IIA) or the protonated-Neutral (IIB) species (Chart 1).



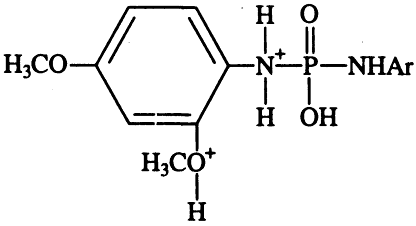
(I) Zwitter ionic (or modified-neutral) species

(II A) neutral species



(II B) Protonated-neutral species

(III) Conjugate acid species



(IV) Protonated-conjugate acid species

Chart 1. Theoretically possible reactive species of the phosphoric-bis-2,4-dimethoxyphenyl amide

A rate maximum observed at 4.0 M HCl has been assigned to the maximum protonation of the moderately-basic phosphoric diamide under observation. The calculated rates via the conjugate acid form (III) (Chart 1) using eq. (5) resemble the observed rate value at 4.0 M HCl.

At 5.0 M HCl and beyond, *i.e.*, up to 7.0 M HCl, the rates are both low as well as constant than those at 4.0 M HCl, and are contributed by form (III), *i.e.*, the conjugate acid species. These rates require the consideration of the water activity term which becomes significant in higher acid (>4.0 M HCl) media. The rates are therefore calculated here on the basis of Bronsted-Bjerrum[7] eq. (6) given as under:

$$k_e \text{ (calcd.)} = k^{+}_{H_0} \cdot C^{+}_{H} \cdot e b'^{+}_{H} \mu \log (aH_2O)_n \qquad (6)$$

The rates thus calculated at and above 5.0 M HCI require the involvement of nearly three water molecules for protonation, the formation of transition state[8] and also the hydrolysis of the phosphoric diamide. Table-1 includes these values, which are also found to resemble the k_e (obsd.) values between 5.0–7.0 M HCl.

In higher acid media, Hammett[9] plot (slope = 0.54), Zucker-Hammet[10] plot (0.83), Bunnett[11] plots (w = 9.61 and w* = 4.84) all favour a bimolecular mode of hydrolysis for the present diamide. Bunnett and Ölsen[12] plot ($\phi = 0.72$) suggests that water acts as both a proton-transfer medium as well as a second reactant during the present hydrolysis. Yates and McCleland[13] plot with slope (r = 3.53, cf. n of log $(aH_2O)_n$, Table-1) recommends the participation of nearly 3–4 water molecules during hydrolysis.

Concentration effect studies were conducted by making the concentration either half or double the normal value. The rates here are as expected, confirming the order to be two. During reagent (nucleophilic) effect studies the rates have been found to follow the order given as below:

Reagent/Condition: Cl^- I^- F^- Br^-; Aq.

K_e L mol^{-1} min^{-1}: $0.03 > 0.02 \approx 0.02 > 0.01; \gg 0.0025$

As compared to the aqueous medium itself, the rates have been found to be promoted by nearly 12, 8 and 4 times respectively. On the other hand, at 0.1 M HCl (0.17 L mol^{-1} min^{-1}) the rates have been found to increase by 10-fold in the presence of imidazole (0.01 M; k_e = 1.67 L mol^{-1} min^{-1}), a strongly basic substrate. Since there is an increase by the use of both moderate and strong nucleophiles, a bimolecular mode of hydrolysis is arrived at for the present compound. Such a mechanism is observed to involve the formation of a transition state[8], which can be ascertained on the basis of solvent polarity changes, too.

Variation in the percentage of acetic acid in acetic acid-water mixture between 10 to 90% was made and the rates (1.0 M HCl) did not vary up to 30% AcOH although they increased by 10-fold in 90% $AcOH-H_2O$ (k_e = 1.62 L mol^{-1} min^{-1}) medium. This clearly supports the formation of a polar transition state resulting from the bimolecular hydrolysis of the neutral species at and beyond 1.0 M HCI (Chart 3(a)).

During the hydrolysis at 1.0 M HCl, effect of parent amine was followed kinetically. In this case the rates were decreased (k_e = 0.15 L mol^{-1} min^{-1}) slightly only, indicating the hydrolysis to be unaltered by the nucleophilic nature of product formed during hydrolysis.

Temperature effect studies between 40 to 60°C were made and Arrhenius[14] parameters determined (Table-2) at 1.0 M HCl. These parameters again favour the bimolecular mode of hydrolysis for the present phosphoric bis-amide under observation. A very low and positive entropy of activation (0–10 e.u.) suggests the formation of a compact transition state (Charts 2–4) during hydrolysis of the ester, mainly as its neutral form.

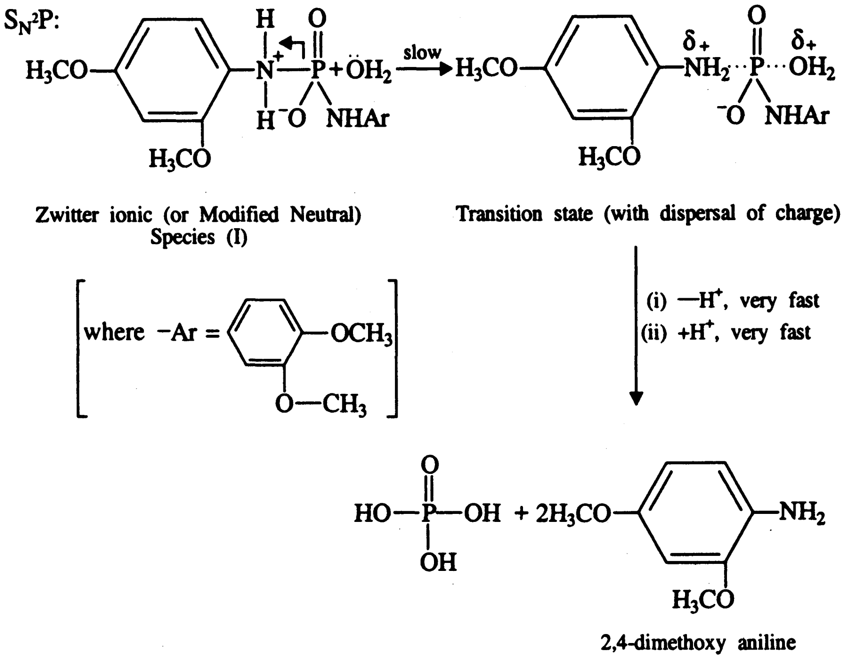


Chart 2. Bimolecular nucleophilic substitution of the zwitterionic (or modified-neutral) species with P-N bond Fission

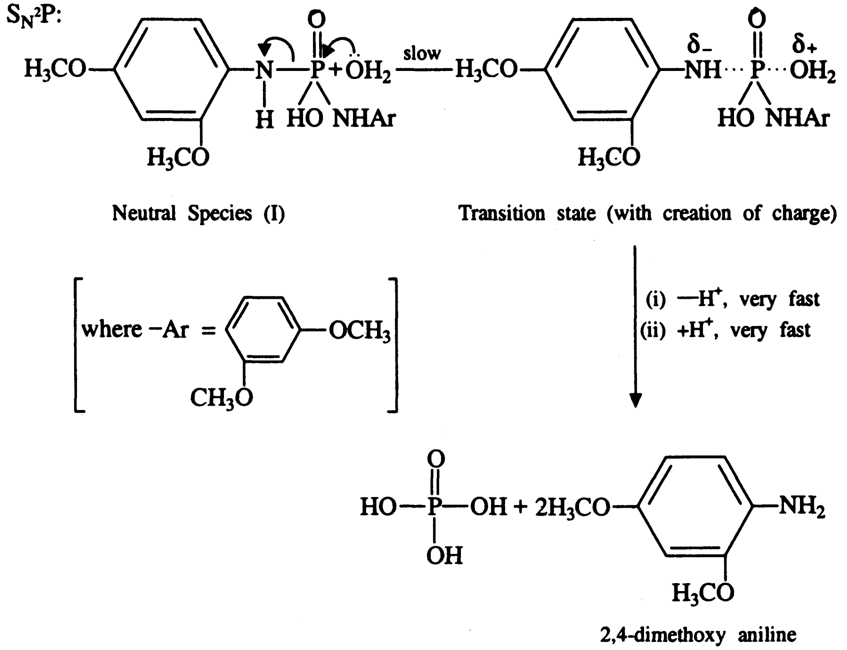


Chart 3. (a) Bimolecular nucleophilic substitution of the neutral species with P-N bond fission

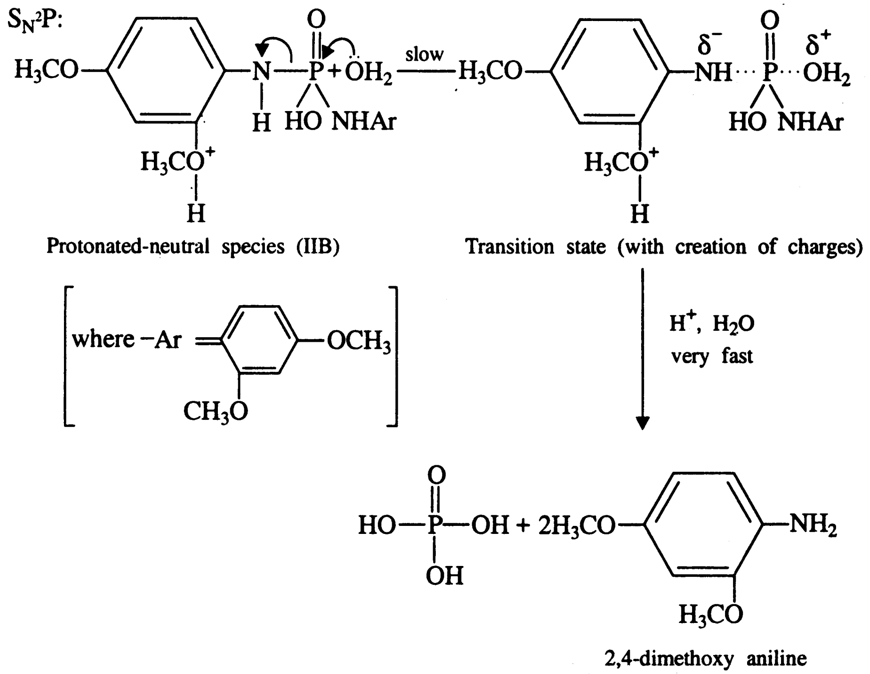


Chart 3. (b) Bimolecular nucleophilic substitution of the protonated-neutral species with P-N bond fission.

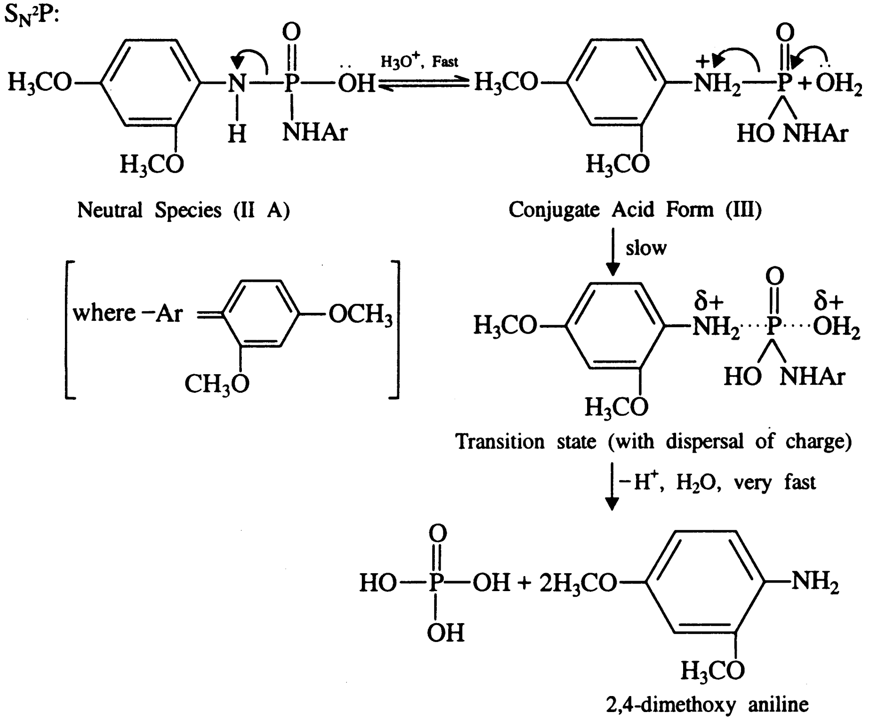


Chart 4. Bimolecular nucleophilic substitution of the conjugate acid species with P-N bond fission.

TABLE-2
ARRHENIUS PARAMETERS FOR THE HYDROLYSIS OF PHOSPHORIC BIS-(2,4-DIMETHOXYPHENYL AMIDE) CHLORIDE AT 1.0 M HCl

E	A	$\Delta S^{\#}$	$\Delta H^{\#}$	$\Delta G^{\#}$
76.35 kJ/mole	5.78×10^9 sec^{-1}	0.33 e.u.	73.76 kJ/mole	73.74 kJ/mole

Nature of bond fission has been decided using the qualitative test[15] (azo-dye[15] test). A positive azo-dye test during the progress of acid hydrolysis is indicative of the P—N bond fission in the present diamide.

On the basis of various effects during kinetics of the hydrolysis 3 reactive species, bimolecularity and P—N bond fission have been decided. Based on the five (Chart 1) reactive species and other aspects, only three (Charts 2–4) reaction mechanisms have been arrived at.

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(*Received:* 12 June 2002; *Accepted*: 14 August 2002) AJC-2821