Hydrolytic Reactivity of an Active Synthetic C-N-P Ester Leading to its Highly Basic Nature

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Hydrolysis of synthetic *bis*-(*m*-MeO-phenyl) phosphoricamide chloride when performed in the acid range, 0.01-7.0 M HCl at 40 ($\pm$ 0.5) ºC in 4 % AcOH-H$_2$O medium gives 1st-order rate coefficients. Ionic strength effect study reveals the contribution of: neutral better named here as protonated-neutral species (0.01-0.10 M HCl) and conjugate acid species (0.5-7.0 M HCl) showing a regular rate increase even between 4.0-7.0 M HCl. The latter behaviour is assigned to the highly basic nature of the present member, making it comparable to the strongly basic amides. The hydrolysis is remarkably promoted by the action of nucleophilic bromide ions [S$_E$2(P)].

Key Words: Hydrolysis, Protonated-neutral species, Conjugate acid species and phosphorylation.

INTRODUCTION

Organic phosphoramidates bearing C-N-P linkage/s in them are known to possess some different features[1] making them commercially viable. Both phosphates (C-O-P) and phosphoramidates (C-N-P) are widely used as prodrug moieties to enhance water solubility[1] or therapeutic potential of a parent drug[2-5]. Their use as drugs in deadly diseases[2,3] like AIDS and cancer, *etc.*, makes them extremely valuable for human use and this change is only brought about by the replacement of O in C-O-P by an N to form C-N-P linkage/s.

EXPERIMENTAL

In order to synthesize *bis*-(*m*-MeO-phenyl) phosphoric amide chloride, *m*-anisidine was phosphorylated by stirring (1:1) with POCl$_3$ in benzene (dry) in the presence of a cationic surfactant[6] (CTAB) at room temperature for *ca.* 0.5 h. Out of the two, the lower violet layer on separation and standing was converted into a light-pink solid. The latter when recrystallized with CHCl$_3$, gave a compound with sharp m.p. of 224-225 ºC. Quantitative elemental analysis (P = 9.49 % as required), IR (P = 0, 1271.66 cm^{-1}) and ^{1}H NMR spectral[7,8] data have proved its identity.

Kinetic study during hydrolysis of the phosphoro-diamidate was made using Allen's modified method[9], for quantitative estimation of phosphorus liberated as (HO)$_2$P(O)NH$_2$/ H$_3$PO$_4$. Optical density measurements were made with Spectronic-20 instrument.

RESULTS AND DISCUSSION

m-MeO-phenyl phosphorodiamidic chloride has been examined in the acid range 0.01-7.0 M HCl in 4 % AcOH-H$_2$O (v/v) at 40 ($\pm$ 0.5) ºC. The rate maximum at 2.0 M HCl is assigned to the formation of the conjugate acid species (II) from the protonated neutral form; while below this *i.e.*, between 0.01-0.1 M HCl, presence and participation of protonated-neutral form (I) with a proton- sit on -OCH$_3$ oxygen atom is decided. 1st order rate coefficients were determined through the kinetic study.

The effect of neutral electrolyte was studied[10] (Fig. 1) using LiCl with HCl and suitable compositions of these when examined, led to the value of 4 + log k$_{Ho}^+$ = 1.60 and b'$_H^+$ = + 0.031. The second empirical term of the Debye-Hückel equation[11] was employed, so that:

$$k_e(\text{calcd}) = k_H^+ \cdot C_H^+ \exp b_H^+ \mu \qquad (1)$$

where, k$_H^+$, C$_H^+$ and b$_H^+$ correspond to the specific acid-catalyzed rate, concentration of H$^+$ and constant/slope of the linear curve, respectively. The calculated rates did not require inclusion of the contribution *via* the neutral species. Table-1 comprises of this data and the rates thus, calculated resemble the observed rate co-efficients *via* the single reactive form between 0.5-7.0 M-HCl, which also supports the validity of the eqn. 1 as above.

Since the compounds belongs to the class of highly basic substrates (*e.g.*, amides) a special Bunnett plot is drawn between log k$_e$ and log ^{a}H$_2$O, giving a slope (w = 2.86).

(I) PROTONATED- NEUTRAL SPECIES

(II) CONJUGATE ACID SPECIES

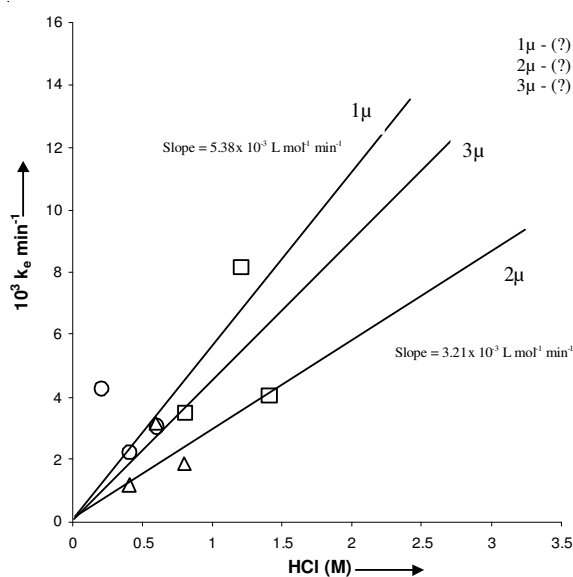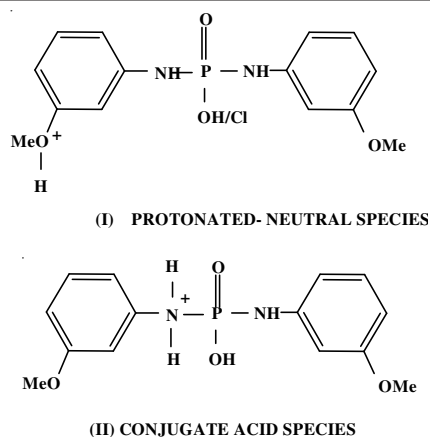Fig. 1.   Kinetic study of the hydrolysis of *bis*-(*m*-MeO-phenyl) phosphoric amide at constant ionic strengths (μ) at 4 % AcOH-H$_2$O mixture at 40 (± 0.5) ºC

TABLE-1

OBSERVED AND CALUCLATED RATE COEFFICIENTS FOR THE HYDROLYSIS (4 % AcOH-H$_2$O) OF *bis*-(*m*-MeO-PHENYL) PHOSPHORIC AMIDE AT 40 (± 0.5) ºC

HCl (M)	$10^3\, k_{H}^{+}\cdot C_{H}^{+}$ (min^{-1})	$10^3 k_e$ (calcd.) (min^{-1})	$10^3 k_e$ (obsd.) (min^{-1})
0.01	0.04	0.04	2.03
0.10	0.40	0.40	1.09
0.50	2.06	2.06	1.80
1.00	4.28	4.28	4.58
2.00	9.18	9.18	7.68
3.00	14.79	14.79	4.50
4.00	21.18	21.18	15.93
5.00	28.44	28.44	31.98
6.00	36.64	36.64	35.86
7.00	45.92	45.92	48.75

Note: k_e obsd. (2.57 × 10^{-3} min^{-1}) in 4 % AcOH-H$_2$O mixture alone at 40 (± 0.5) ºC and are a little h higher those at 0.5 M HCl.

Similarly, the application of the hydration parameter treatment (or Yates and McCleLand plot) gives 'r' (slope) as 2.94. Similarity of 'w' with 'r' is valuable and postulates the involvement of almost three molecules of water in the slow step during hydrolysis. On this basis, the hydrolytic breakdown of *bis*-(*m*-MeOphenyl)phosphoricamide chloride in the acid medium thus requires water as a nucleophile, second reaction partner and a proton-transferring H$_3$O$^+$ agent as well.

Arrhenius parameters[10] had been determined for the hydrolysis of *m*-MeO-phenyl phosphorodiamidate, from rates at 0.1 M HCl at three varied temperatures. The calculated parameters (Table-2) include low E value, high frequency factor (A), $\Delta S^{\neq}$, the entropy of activation, a high negative value again; low enthalpy of activation $\Delta H^{\neq}$ and a high +ve free energy ($\Delta G^{\neq}$). These values indicate that the activated complex is less probable. The reaction is governed by both A and $\Delta S^{\neq}$ values but, however, not activation controlled. The formation of transition state with water is justified on the basis of above data along with the bimolecular nature of hydrolysis.

Solvent effect study[11] during hydrolysis was made in 4 % (4.58 × 10^{-3} min^{-1}),16 % (4.02 × 10^{-3} min^{-1}) and 91 % (10.38 × 10^{-3} min^{-1}) AcOH-H$_2$O. It shows an increase in rates by nearly two times only at the much higher percentage, at 1.0 M HCl. It thus favours reaction involving protonation due to the lowering of the dielectric constant in such a medium. Therefore, the transition state is formed and supported with dispersal of positive charge. A similar study when performed in 16 % DMF-H$_2$O, the rates are lowered (2.38 × 10^{-3} min^{-1}) in comparison to those in 16 % AcOH-H$_2$O mixture. With 32 % DMF-H$_2$O, however the rates (19.11 × 10^{-3} min^{-1}) are elevated by nearly eight times, which is ascribed to the basic and dipolar aprotic nature[12] of the solvent used, leading to justification of the transition state with dispersal of the +ve charge, *via* the conjugate acid species.

An important study included the effect of nucleophilic reagents[13] on the hydrolysis at 0.1 M HCl, giving the following order of reactivity:

Nucleophilic reagents: Br' >> Cl' > I' > F' > H$_2$Ö
$10^3 k_e$ min^{-1}:   ∞   6.35 3.45 1.40 1.28
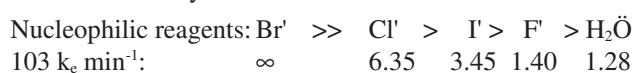
The extraordinarily higher rates of hydrolysis in the presence of bromide ions may be accounted for by the elimination, S$_E$2(P), rather than substitution, S$_N$2(P), mechanism of hydrolysis of the diamidate by the attack of strongly nucleophilic Br' ions. On the other hand, F', I' and Cl',gradually and continuously increase the rates of the bimolecular hydrolysis, in this order.

Effect of concentration change to half (4.0 × 10^{-4} M) of the phosphorodiamidate leads to almost half magnitude of the rates (2.32 × 10^{-3} min^{-1}) as well and thus supports first order rate data. Making the concentration double (16.0 × 10^{-4} M) brings about a little change (4.58-5.60 × 10^{-3} min^{-1}) only in

TABLE-2

ARRHENIUS PARAMETERS

Energy of activation 'E'	Frequency factor 'A'	Entropy of activation $\Delta S^{\neq}$	Enthalpy of activation $\Delta H^{\neq}$	Free energy $\Delta G^{\neq}$
1.64 Kcal mol^{-1} or 6.85 KJ mol^{-1}	4.28 × 10^{18} sec^{-1}	-49.11 e.u. or -49.11 cal mol^{-1}	1.02 Kcal mol^{-1} or 4.26 KJ mol^{-1}	16.39 Kcal mol^{-1} or 68.51 KJ mol^{-1}

the rate value than the normal concentration. This study thus favours first order for the hydrolysis of the *bis*-phosphoric amide.

During the hydrolysis, the parent amine *i.e.*, *m*-anisidine, was expected to be generated and also to catalyse the reaction due to its nucleophilic nature. Addition of both half (4.0×10^{-4} M) and an identical (8.0×10^{-4} M) concentration of *m*-anisidine, gave almost similar rates and these are found to remain unaffected by such a change. Therefore, interference by the liberated nucleophile was negligible.

Arrhenius and other kinetic parameters, suggest a P-N bond fission[14] to occur during hydrolysis, which is also decided by an azo-dye test of the product only qualitatively during the progress of hydrolysis. The overall hydrolytic rate coefficients' data when compared with the related members with MeO-group in *ortho*- and *para*-positions, the present compound shows the least reactivity. This may be justified by absence of a direct interaction of the lone pair on *m*-MeO-group with the C-N-P linkage.
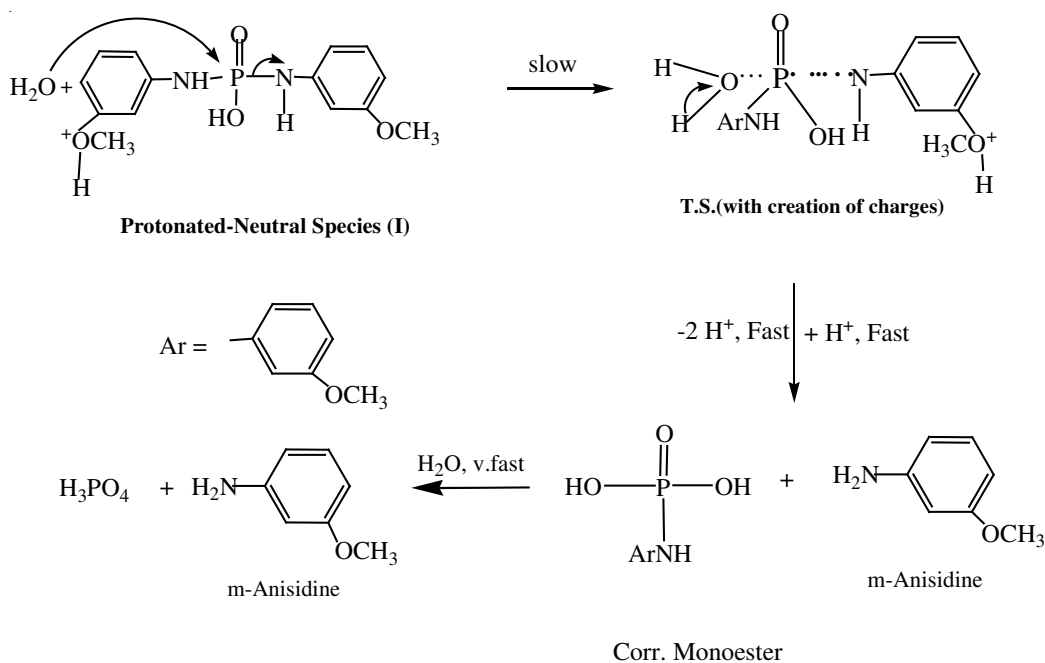

Protonated-Neutral Species (I)   **T.S.(with creation of charges)**

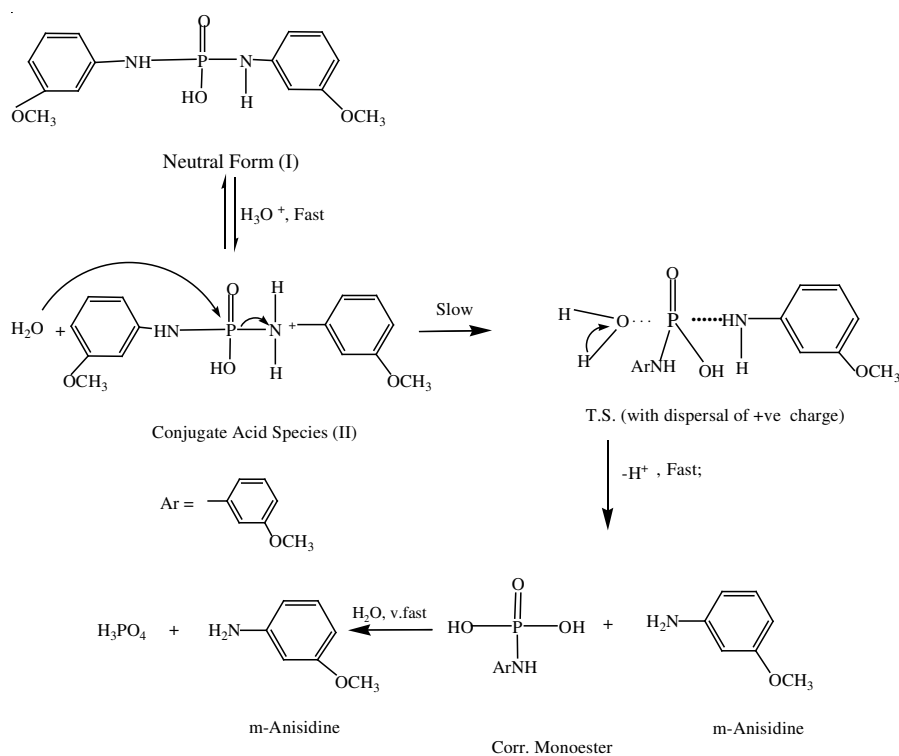Chart 1: S_N^1(P)-Hydrolysis of *bis*-(*m*-MeO-phenyl)phosphoric amide *via* the protonated-neutral species (I) inlow acid medium

Chart 2: S_N^2(P) Hydrolysis *via* the conjugate acid species (II) inacid medium of *bis*-(*m*-MeO-phenyl) phosphoric amide
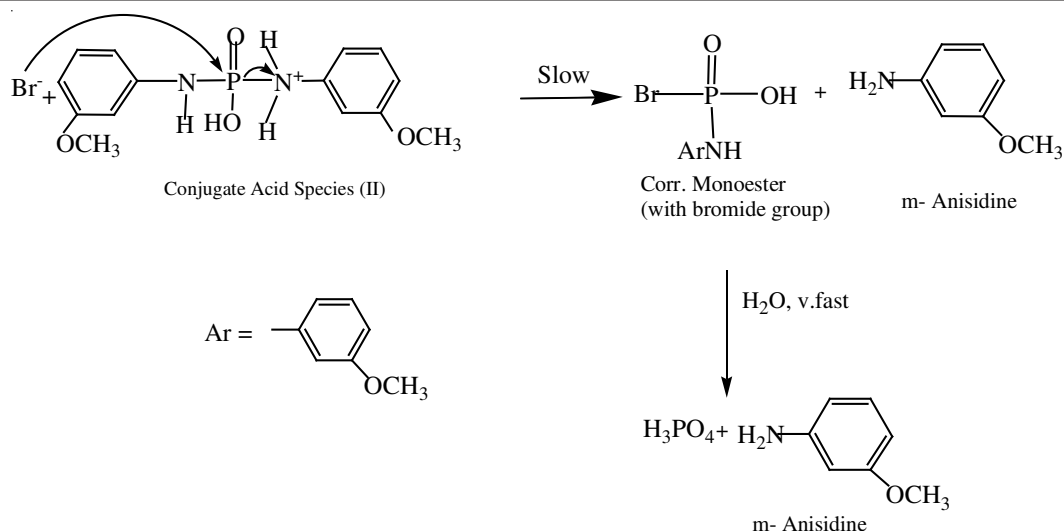
Chart 3: $S_E^2(P)$-Nucleophilic attack of the bromide ions on the conjugate acid species (II) of *bis*-(*m*-MeO-phenyl) phosphoric amide

Conclusion

From all the above information, it is decided that *bis*-(*m*-MeO-phenyl) phosphoric amide undergoes acid (0.01-7.0 M HCl) hydrolysis *via* the protonated neutral(I) and the conjugate acid species(II) and these are shown in Charts 1 and 2. The 3rd mechanism, $S_E 2(P)$, *via*. the attack of bromide ions is included in Chart 3. A new conjugate acid form (III) can also be created *via* the formation of the protonated neutral species (I) of the *bis*-phosphoric amide. It will again follow a similar route to that of conjugate acid form(II), so that two molecules of the parent amine and one molecule of H_3PO_4 again is liberated.
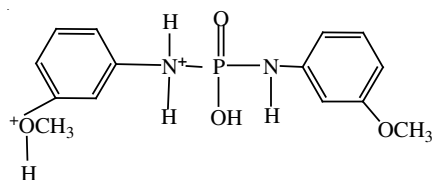
(III) Conjugate acid species of the protonated-neutral form

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