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Acid Catalyzed Hydrolysis of Di-2-Methoxy-4-Nitroaniline Phosphate

Chemistry

KEYWORDS : Hydrolysis, Di-2-methoxy-4-nitroaniline phosphate, Ionic strength, P-N bond fission.

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ABSTRACT

The hydrolysis of phosphate esters is one of the most fundamental chemical and biochemical reaction and their kinetic study deals all the significant aspects of chemical reactions including mechanism. In present investigation hydrolytic study of di-2-methoxy-4-nitroaniline phosphate has been carried out in 0.5-7.0 mol dm-3 HCl in 20% (v/v) dioxane-water medium at 70oC. The inorganic phosphate produced during hydrolysis has been determined spectrophotometrically using Allen's modified method. The pseudo first order rate constants have been determined. The log rate profile shows rate maximum at 4.0 mol dm-3 HCl. The lowering of rate after 4.0 mol dm-3 HCl has been attributed to the effect of water activity. Ionic strength data is used to identify reactive species and find out theoretical rates. Bimolecular nature of the reaction has been decided by the Arrhenius, Bunnett & Bunnett-Olsen's parameters and Zucker-Hammett hypothesis. The diester involves P-N bond fission, which is strengthened by comparative kinetic rate data. The probable reaction mechanism for the hydrolysis of diester via conjugate acid species has been suggested.

Introduction

Organophosphate esters are the derivatives of orthophosphoric acid, which can in principle be esterified at any or all of three different positions, forming monoesters, diesters and triesters and the reaction mechanism will vary according to the system[1]. Organophosphates having C-N-P linkage is of great importance and display a significant role in various fields[2]. These compounds are the essential constituents of protoplasm, DNA and play a fundamental role for many important functions e.g. Nucleotides, genetic information, photosynthesis.[3-6] Phosphonate containing drugs are increasingly being explored in many therapeutic areas[7]. The extreme toxicity, broad-spectrum activity and low cost of organophosphorus compounds have made them popular as pesticides, insecticides, bactericides and antibiotics[8, 9]. Phosphate ester hydrolysis is a crucially important reaction in biological systems, being involved in biosynthesis processes. Hydrolytic reaction of phosphate ester is now a subject of kinetic study due to its versatile applications in different area of chemistry[10]. Keeping this in view the kinetics of the hydrolysis of di-2-methoxy-4-nitroaniline phosphate has been investigated.

Experimental

2.1 Materials and Methods

Di-2-methoxy-4-nitroaniline phosphate was synthesized by the method of Rudert[11]. All the reactions were carried out at 70 ± 0.5oC employing 5.0 x 10^{-4} mol dm-3 concentration of the diester in 20% (v/v) dioxane-water medium. The constant ionic strength was maintained by appropriate mixture of HCl and NaCl. The progress of the kinetics of hydrolysis of di-2-methoxy-4-nitroaniline phosphate was followed by estimation of inorganic phosphate, using Allen's modified method[12] spectrophotometrically. All the chemicals used were of A. R. grade.

Results and Discussion

3.1 Hydrolysis via Conjugate Acid Species

The rate of hydrolysis of di-2-methoxy-4-nitroaniline phosphate was carried out at 70°C in the range of 0.5 to 7.0 mol dm^{-3} HCl in 20% (v/v) dioxane-water medium. The pseudo-first order rate constants are summarized in Table-1. From the results, it may be seen that the rate of reaction increases with the increase in acid molarity up to 4.0 mol dm^{-3} HCl. The maximum rate at 4.0 mol dm^{-3} HCl was attributed to the complete conversion of the substrate into its conjugate acid species. The decrease in the rate after 4.0 mol dm^{-3} HCl was attributed to the lowering of concentration of attacking nucleophile taking part in reaction, i.e., due to variation in water activity.

3.2 Effect of Ionic Strength

Hydrolysis at constant ionic strength shows that the reaction proceeds via both neutral and conjugate acid species. The plot of rate constants against acid molarity at each ionic strength is linear (Figure-1). The linearity of the plot with positive slope represents the acid catalyzed reaction and since the slope of the linear plot increases with increase in ionic strength, the hydrolysis via conjugate acid species exhibits positive salt effect. All the lines meet at different points on the rate axis, indicating the participation of neutral species. Different values of intercepts show that the contribution of neutral species at different acidities is varying.

From the study of ionic strength effect, the total rates contributed by conjugate acid and neutral species may be calculated by the following second empirical term of Debye-Huckle equation13.

$$k = k_{H^+} . C_{H^+} + k_N \qquad (1)$$

In the above equation the terms k, k_{H^+} and k_N are experimental rate constants, the specific acid catalyzed rates and specific neutral rates at that ionic strength respectively. Specific acid-catalyzed rates (k_{H^+}) were then converted into acid rates (k_{H^+}. C_{H^+}) as :

$$k_{H^+} . C_{H^+} = k_{Ho^+} . C_{H^+} . \exp . b'_{H^+} . \mu \qquad (2)$$

Where for HCl, μ and C_{H^+} are of the same value. The slope of the linear curve is b'_{H^+}, which is equal to $b'_{H^+}/2.303$ and intercept on the log rate axis is $3^{+} \log k_{Ho^+}$ (Fig. not shown). The sum of neutral and acid rates agrees well with the experimentally observed rates (Table-1) up to 4.0 mol dm^{-3} HCl. In the region of 0.5 to 4.0 mol dm-3 the rate law is calculated by equation:

$$k = 14.45 \times 10^{-3} . C_{H^+} . \exp (0.02 \times 2.303) \mu + 3.55 \times 10^{-3} \exp (0.18 \times 2.303) \mu \qquad (3)$$

The lowering in rates in 5.0, 6.0, 7.0 mol dm^{-3} HCl can be explained by considering water activity as an additional parameter represented as:

$$k = k_{Ho^+} . CH^+ \exp b_{H^+} . \mu (aH_2O)n + k_N . \exp . b'_N . \mu (aH_2O)^n \qquad (4)$$

Where n is an integer and $(aH_2O)n$ is water activity14. Hence the rate laws beyond 4.0 mol dm^{-3} HCl were calculated employing the Bronsted - Bjerrum eqution15:

$$k = 14.45 \times 10^{-3} . CH^+ . \exp (0.02 \times 2.303) \mu (aH_2O)n + 3.55 \times 10^{-3} \exp .$$

$$(0.18 \times 2.303) \mu (aH2O)^n \qquad (5)$$

The revised estimated rates agree well with the experimentally observed rates (Table-1). It is clear from the above result that di-2-methoxy-4-nitroaniline phosphate in acid solution occurs via both conjugate acid and neutral species and their rates are subjected to both ionic strength and water activity.

Table – 1 Estimated and experimental rates for the hydrolysis of di-2-methoxy-4-nitroaniline phosphate at 70°C

HCl (mol dm^{-3})	$k_{H^+}.C_{H^+}\times10^3$ (min^{-1})	$k_N\times10^3$ (min^{-1})	$k\times10^3$ (min^{-1})	-log $(a_{H2O})^n$	$k\times10^3$ (min^{-1}) Estd.	$k\times10^3$ (min^{-1}) Expt.
0.5	7.41	4.36	11.77	-	11.77	11.23
1.0	15.14	5.37	20.51	-	20.51	21.06
1.5	23.44	6.61	30.05	-	30.05	32.27
2.0	31.62	8.13	39.75	-	39.75	37.51
2.5	40.74	10.00	50.74	-	50.74	49.13
3.0	50.12	12.30	62.42	-	62.42	63.98
3.5	58.88	15.13	74.01	-	74.02	73.91
4.0	69.50	18.62	88.12	-	88.12	86.84
4.5	79.43	22.91	102.34	(0.13)	75.78	78.50
5.0	91.20	28.18	119.38	$(0.16)^2$	57.14	55.38
6.0	114.81	42.66	157.47	$(0.21)^3$	36.91	38.15
7.0	141.25	64.56	205.81	$(0.28)^4$	15.61	18.84

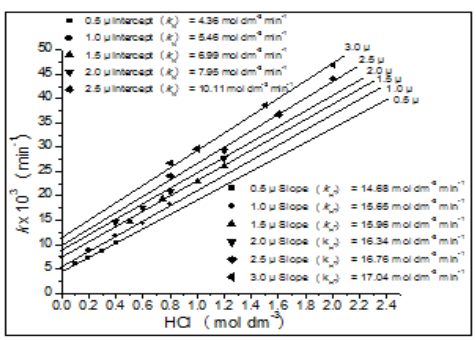

Figure-1 Acid catalyzed hydrolysis of di-2-methoxy-4-nitroaniline phosphate at constant ionic strength at 70°C

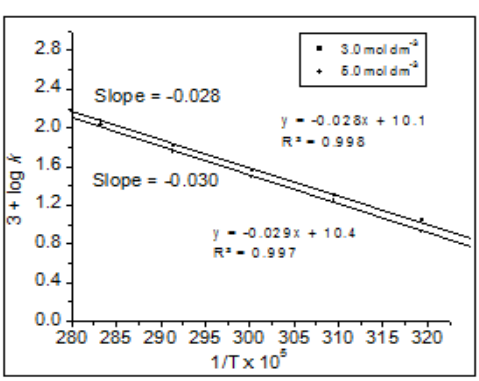

Figure-2 Arrhenius plot for the hydrolysis of di-2-methoxy-4-nitroaniline phosphate

3.3 Molecularity of Reaction

Arrhenius parameters are determined for the hydrolysis at 3.0 and 5.0 mol dm^{-3} HCl (Table-2 & Figure-2). The magnitude of the Arrhenius parameters fall in the range of bimolecular reaction16. Bimolecular nature of reaction is further supported by plots of Zucker-Hammett17 (1.03), Hammett18 (0.52) and Bunnett (ω =8.95, ω* = 3.34). Bunnett-Olsen19 parameter (φ =1.04) (plots not shown) suggested that water is involved as a proton transfer agent in the rate determining step.

Table-2 Arrhenius parameters for hydrolysis of di-2-methoxy-4-nitroaniline phosphate at 70°C

HCl (mol dm^{-3})	Parameters		
	E (Kcal mol^{-1})	A (sec^{-1})	$-\Delta S^{\neq}$ (e. u.)
3.0	12.81	9.33 X 10^6	28.92
5.0	13.73	3.09 X 10^7	26.54

For determination of kinetic order, a series of kinetic runs with different substrate concentrations (2.5, 5.0 x 10^{-4}, 1.0 x 10^{-3} mol dm^{-3}) have been performed at 3.0 mol dm^{-3} HCl in 20% (v/v) dioxane-water medium at 70°C and obtained first order rate constants, k (63.12, 63.98, 64.02 min^{-1}). The results show that the rate constants are independent of substrate concentrations. Thus the solvolytic reaction proceeds via pseudo first order reaction.

Solvent effect has been studied using different dioxane mixture. The effect of solvent (Table-3) shows a significant rise in rates; dioxane being a better proton donor than water increases the concentration of conjugate acid species resulting in the increased rates. Effect on the rate of hydrolysis may, therefore, be taken to indicate the formation of transition state in which charge is dispersed and this is accordance with Chanley's observation[20].

Table –3 Solvent effect rate data for the hydrolysis of di-2-methoxy-4-nitroaniline phosphate

% of Dioxane (v/v)	HCl (mol dm^{-3})	$k\times10^3$ (min^{-1})	HCl (mol dm^{-3})	$k\times10^3$ (min^{-1})
0.00	3.0	63.98	5.0	55.38
10.0		69.41		61.21
20.0		74.63		65.87
30.0		79.78		70.86
40.0		83.89		74.79

Di-2-methoxy-4-nitroaniline phosphate may undergo hydrolysis either by P-N or C-N bond fission. The kinetic rate data for the isokinetic relation21, 22 have been summarized in Table-4. The point of di-2-methoxy-4-nitroaniline phosphate lies on the linear curve of those diesters which are known to undergo hydrolysis via P-N bond fission (Figure-3). Thus P-N rather than C-N bond fission appears to be more likely.

Table-4 Comparative kinetic rate data for hydrolysis of some phosphate diesters via conjugate acid species

Sr. no.	Phosphate Diesters	Medium HCl (mol dm^{-3})	E (Kcal/mole)	$-\Delta S\neq$ (e. u.)	Molecularity	Bond fission
1.	Cyclohexyl amine phosphate	3.0	12.09	37.11	2	P-N
2.	2-Methoxy-4-nitroaniline phosphate	3.0 5.0	12.81 13.73	28.92 26.54	2* 2*	Present work
3.	o-Toluidine phophate	1.0	11.40	38.66	2	P-N
4.	p-Phenatadine phosphate	3.0	5.72	70.55	2	P-N
5.	m-Toluidine phosphate	3.0	15.56	21.29	2	P-N
6.	2-Chloroaniline phosphate	3.0	13.70	28.90	2	P-N

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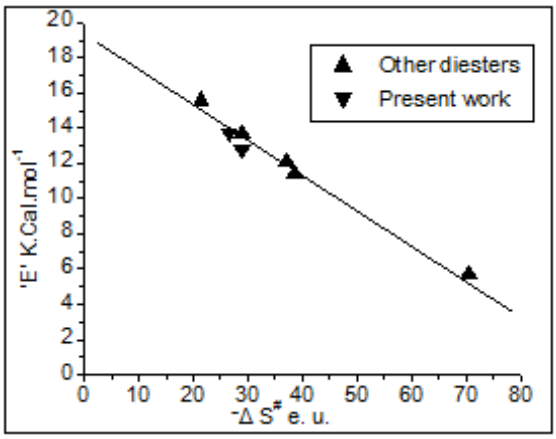
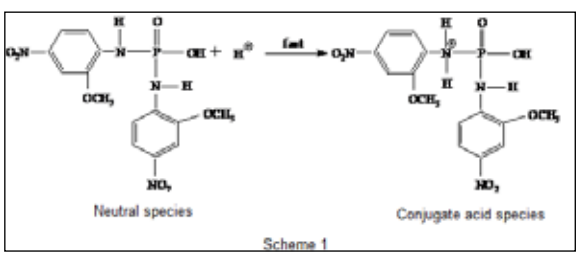


Figure-3 Isokinetic relationship plot for the hydrolysis of some phosphate diesters via conjugate acid species

3.4 Mechanism

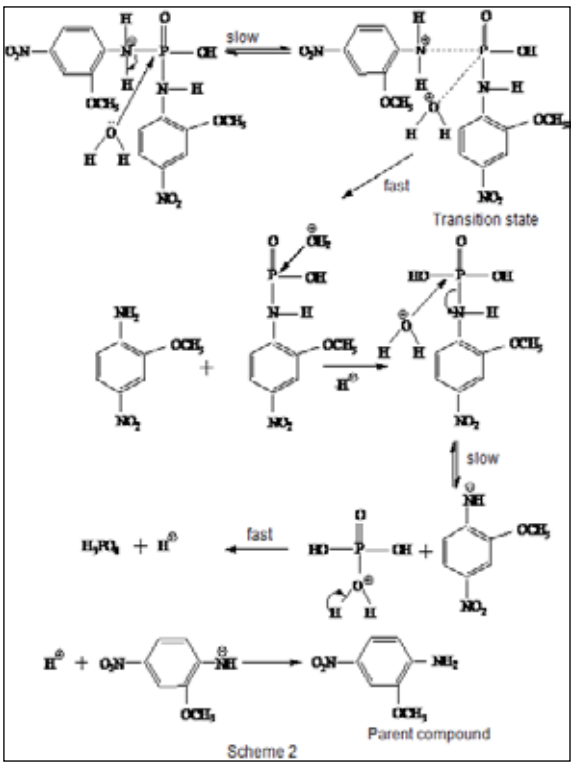
On the basis of experimental results, the probable reaction mechanism of the acid-catalyzed hydrolysis of di-2-methoxy-4-nitroaniline phosphate via conjugate acid species may be as shown by scheme 1 and scheme 2:

(a) Formation of conjugate acid species:



Scheme 1

(b) Bimolecular nucleophilic attack of water on phosphorous via conjugate acid species S_N^2 (P):



Scheme 2

Conclusions

In the region 0.5 to 7.0 mol dm^{-3} HCl di-2-methoxy-4-nitroaniline phosphate has been found to hydrolyze via neutral and conjugate acid species. The acid catalyzed hydrolysis is subjected to positive effect of ionic strength. Bimolecular nature of hydrolysis has been supported by different parameters such as Bunnett, Bunnett-Olsen, Arrhenius and Hammett, Zucker-Hammett hypothesis etc. Comparative kinetic rate data of other diester has supported the P-N bond fission. The probable S_N^2 (P) mechanism was suggested for the hydrolysis via conjugate acid species.

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