

Research Article

Hydrolysis of Mono-N-Ethyl-*o*-Toluidine Phosphate-Catalyzed by Hydrochloric Acid

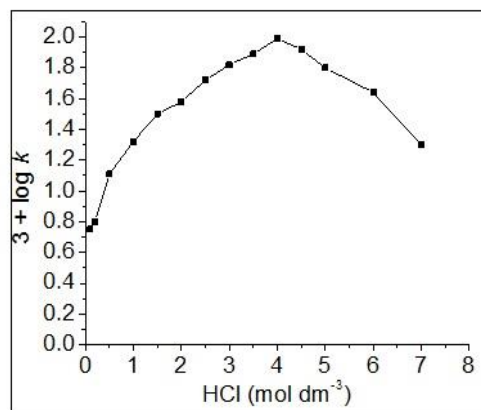
Homeshwari Yadav and S. A. Bhoite*

School of Studies in Chemistry, Pt. Ravishankar Shukla University, Raipur- 492010, Chhattisgarh India.

Abstract

Hydrolysis of mono-N-ethyl-*o*-toluidine phosphate has been carried out in 0.1-7.0 mol dm⁻³ hydrochloric acid in aqueous medium at 50 ± 0.5°C. The log rate profile shows rate maximum at 4.0 mol dm⁻³ hydrochloric acid. The lowering in rate after 4.0 mol dm⁻³ may be attributed to the lowering in concentration of the nucleophile. The effects of ionic strength, temperature and solvent on the rate of hydrolysis have been studied. Molecularity and order of reaction have been supported by the Arrhenius parameters, Zucker-Hammett hypothesis, Bunnett & Bunnett-Olsen's parameters. The observed rates have been found in close agreement with the estimated theoretical rates derived from the second empirical term of Debye-Huckel equation. Probable reaction mechanism has been suggested for the hydrolysis of monoester.

Keywords: Hydrolysis, Mono-N-ethyl-*o*-toluidine phosphate, Ionic strength, Solvent effect, Molecularity

***Correspondence**

S. A. Bhoite,
Email: sa.bhoite10@gmail.com

Introduction

Phosphate esters play a significant role in the physiology of cells and hence are essential to organism. Most prominent is the participation of phosphate esters as a structural and functional element in DNA, RNA, and its monomeric building blocks, the occurrence as a post translational signal in proteins and as a head group in phospholipids[1]. Phosphate monoesters are even more stable. They take part in compartmentalization and transport regulation of water-soluble metabolites and in lipid membranes [2]. Hydrolysis of phosphate esters is very important reaction in many biological systems [3]. The role of organophosphate esters in many fields is well known; in the life processes of living organisms, as highly effective agents for controlling agricultural pests; as herbicides and defoliant; as drugs for curing various diseases in medicine and veterinary science; and in industry as plasticizers[4] for polymers, hardeners for film and photo materials, different additives in lubricants and hydrocarbon fuels, admixtures for increasing the incombustibility of compounds, antioxidant and extractants [5,6].

The kinetics of reaction of simple organic phosphates provides an insight into more complicated reactions during their metabolism. The determination of mechanism of hydrolysis of organic phosphate is expected to reveal the possible correlations between the reaction path of chemical and enzymatic hydrolysis of biologically important phosphate esters [7]. Thus, the kinetic studies of the hydrolysis of organophosphate esters create great academic interest. The present work concentrates on synthesis of mono-N-ethyl-*o*-toluidine phosphate and their hydrolytic studies under different experimental conditions.

Experimental

Mono-N-ethyl-*o*-toluidine phosphate (Ba-Salt) has been synthesized by Cavalier method [8] in our laboratory. The reactions have been carried out at $50 \pm 0.5^\circ\text{C}$ employing $5.0 \times 10^{-4} \text{ mol dm}^{-3}$ solution of the monoester in aqueous medium. The inorganic phosphate obtained during hydrolysis was estimated spectrophotometrically by Allen's modified method [9]. The constant ionic strength was maintained by using appropriate mixture of HCl and NaCl. All the chemicals used were of AR grade. Pseudo-first-order rate constants were derived from the first-order rate equation.

Results and Discussion

Hydrolysis via conjugate acid species

The hydrolysis of mono-N-ethyl-*o*-toluidine phosphate has been studied at $50 \pm 0.5^\circ\text{C}$ in the range of 0.1 to 7.0 mol dm^{-3} HCl in aqueous medium. The pseudo-first order rate constants are summarized in Table 1 and illustrated by Figure 1. From the results, it may be seen that the rate of reaction increases with increase in acid molarity up to 4.0 mol dm^{-3} HCl and there after it decreases. The maximum rate at 4.0 mol dm^{-3} HCl was attributed to complete conversion of the ester molecule into their respective conjugate acid species. After complete conversion of protonated species, rate should remain constant but it further decreases with the increase in acid molarity. The decrease in the rate is attributed to the lowering of concentration of attacking nucleophile taking part in the reaction, i.e., due to variation in water activity.

Effect of ionic strength

The kinetic runs were made by using adequate mixture of NaCl and HCl at different ionic strength. The rate constants are illustrated by Figure-2. Hydrolysis at each ionic strength is denoted by linear curves that make a positive slope with the acid axis; hydrolysis is subjected to acid-catalysis at each ionic strength. The slope of straight line increases with the increase in the ionic strength. Hence, acid-catalyzed hydrolysis is attributed to the 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 forms may be calculated by the following second empirical term of Debye-Huckel equation [10].

$$k = k_{\text{H}^+} \cdot C_{\text{H}^+} + k_{\text{N}} \quad (1)$$

Where, k , $k_{\text{H}^+} \cdot C_{\text{H}^+}$ and k_{N} are experimental rates, specific acid catalyzed rates, neutral rates and concentration of hydrogen ion $[\text{H}^+]$, respectively. The accelerating ionic effect indicates that mono-N-ethyl-*o*-toluidine phosphate ester undergoes acid-catalyzed hydrolysis with positive effect of the ionic strength. Figure 3 shows the specific acid-catalyzed rates with their logarithmic values at that ionic strength. The slope of the line represents a constant b'_{H^+} , where $b' = b/2.303$, and intercepts on the rate axis represent the specific acid-catalyzed rates ($\log k_{\text{H}^+}$). The linearity of the curve (Figure 3) shows the following relation of the rate constant with ionic strength.

This presents an empirical form of the Debye-Huckel equation:

$$k = k \exp b'_{\text{H}^+} \cdot \mu \quad (2)$$

The specific acid-catalyzed rate may be shown as

$$k_{\text{H}^+} = k_{\text{H}_0^+} \exp b'_{\text{H}^+} \cdot \mu \quad (3)$$

Where, k_{H^+} , $k_{H_0^+}$, b'_{H^+} and μ are specific acid-catalyzed rate at that ionic strength, specific acid-catalyzed rate at zero ionic strength, a constant and ionic strength, respectively. Specific acid-catalyzed rates can be converted into acid-catalyzed rates,

$$k_{H^+} \cdot C_{H^+} = k_{H_0^+} \cdot C_{H^+} \cdot \exp .b'_{H^+} \cdot \mu \quad (4)$$

$$\log k_{H^+} \cdot C_{H^+} = \log k_{H_0^+} + \log C_{H^+} + b'_{H^+} \cdot \mu \quad (5)$$

$$k_N = k_{N_0} \exp b'_N \cdot \mu \quad (6)$$

$$\log k_N = \log k_{N_0} + b'_N \cdot \mu \quad (7)$$

Where k_N is neutral rate and $b'_N = b_N/2.303$.

Equations (5) and (7) may be used for the acid-catalyzed and the neutral rates, respectively, at each experimental rate.

$$k = k_{H^+} C_{H^+} + k_N \quad (8)$$

Table 1 Estimated and experimental rates for the hydrolysis of mono-N-ethyl-*o*-toluidine phosphate at 50°C

HCl (mol dm ⁻³)	$k_{H^+} \cdot C_{H^+} \times 10^3$ (min ⁻¹)	$k_N \times 10^3$ (min ⁻¹)	$k \times 10^3$ (min ⁻¹)	$-\log$ (a _{H2O}) ⁿ	$k \times 10^3$ (min ⁻¹) (Estd.)	$k \times 10^3$ (min ⁻¹) (Expt.)	$3 + \log k$ (Estd.)	$3 + \log k$ (Expt.)
0.1	1.35	3.31	4.66	-	4.66	5.60	1.67	0.75
0.2	2.75	3.47	6.22	-	6.22	6.28	0.79	0.80
0.5	7.08	3.89	10.97	-	10.97	12.87	1.04	1.11
1.0	14.79	4.90	19.69	-	19.69	21.10	1.29	1.32
1.5	23.44	6.03	29.47	-	29.47	31.76	1.47	1.50
2.0	32.36	7.59	39.95	-	39.95	38.14	1.60	1.58
2.5	42.66	9.33	51.99	-	51.99	52.19	1.72	1.72
3.0	53.37	11.75	65.12	-	65.12	66.22	1.81	1.82
3.5	64.57	14.45	79.02	-	79.02	77.67	1.90	1.89
4.0	77.62	18.20	95.82	-	95.82	96.76	1.98	1.99
4.5	91.20	22.65	113.85	(0.13)	84.40	82.42	1.93	1.92
5.0	107.15	28.18	135.33	(0.16) ²	64.76	63.67	1.81	1.80
6.0	141.25	43.65	184.90	(0.21) ³	43.34	43.58	1.64	1.64
7.0	181.97	67.61	249.58	(0.28) ⁴	18.93	19.91	1.28	1.30

Table 1 summarizes both the observed and calculated rates of the hydrolysis in the acid region.

The lowering in rates in 5.0, 6.0, 7.0 mol dm⁻³ HCl may be attributed to the lowering in concentration and participation of water molecules. The rate beyond 4.0 mol dm⁻³ HCl was calculated employing the Bronsted - Bjerrum equation [11]:

$$k = k_{H^+} C_{H^+} (a_{H_2O})^n + k_N (a_{H_2O})^n \quad (9)$$

$$k_{H^+} C_{H^+} = k_{H_0^+} C_{H^+} \exp b'_{H^+} \mu (a_{H_2O})^n \quad (10)$$

$$\log k_{H^+} \cdot C_{H^+} = \log k_{H_0^+} + \log C_{H^+} + b'_{H^+} \mu + n \log (a_{H_2O})$$

The neutral rate at higher concentration is as follows:

$$k_N = k_{N_0} \exp b'_N \mu (a_{H_2O})^n \quad (11)$$

Where $(a_{H_2O})^n$ is water activity term and n is an integer, which increases with increase in acidity. The revised estimated rates agree well with the experimentally observed rates (Table 1). It is clear from the above result that hydrolysis of mono-N-ethyl-*o*-toluidine phosphate in acid solution occurs *via* both conjugate acid and neutral species and their rates are subjected to both ionic strength and water activity.

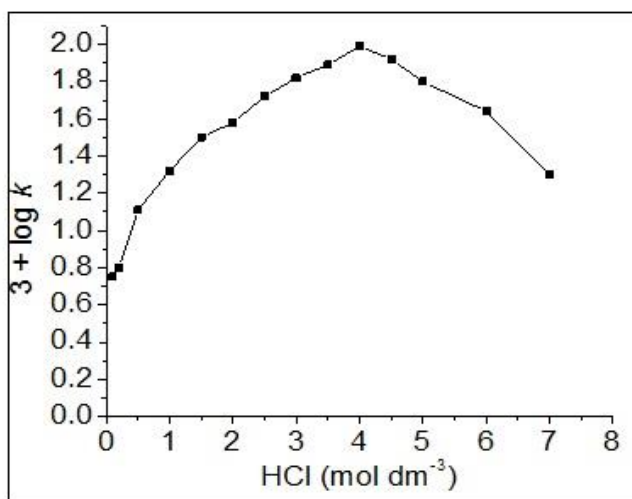


Figure 1 Plot of $3 + \log k$ versus HCl mol dm^{-3} for acidic hydrolysis of mono-N-ethyl-*o*-toluidine phosphate

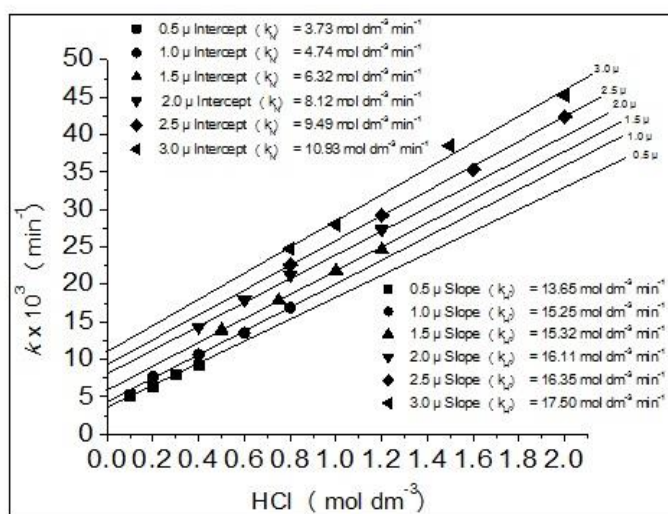


Figure 2 Acid catalyzed hydrolysis of mono-N-ethyl-*o*-toluidine phosphate at constant ionic strength at 50°C

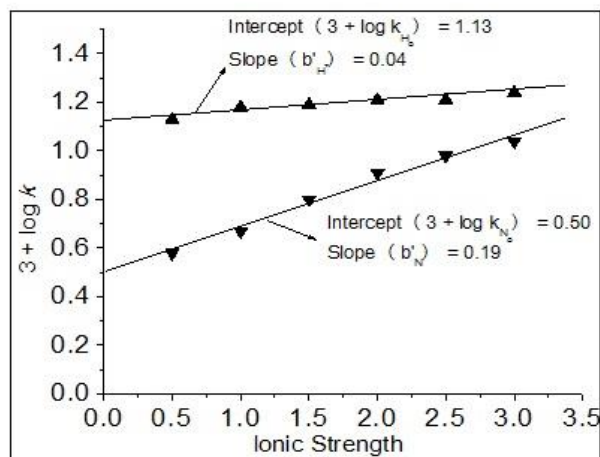


Figure 3 Plot of $3+\log k$ versus ionic strength for acidic hydrolysis of mono-N-ethyl-*o*-toluidine phosphate

Molecularity of reaction

The Zucker-Hammett [12] hypothesis is made up of two parts. In the first part, Hammett [13] postulated that the reaction that give a linear plot of log rate constants against the acidity function ($-H_0$) did not involve water molecules in the rate-determining step. The slope value $0.55 (\pm 0.02)$ (Figure not shown) of the plot is far from unity, indicating the absence of unimolecular hydrolysis. The second part of the hypothesis deals with a plot between the log rate constant and the log acid molarity. A unit or approximately unit slope of this plot was used as a criterion to predict the probable mechanism to be bimolecular, i.e., the reaction involves the participation of water molecule in the transition state. The slope value $1.10 (\pm 0.04)$ (Figure not shown) clearly indicates the bimolecularity of the reaction.

Bunnett [14] put the hypothesis in a modified form and suggested two parameters ω and ω^* . The former is the slope of plot between $\log k + H_0$ vs $-\log a_{H_2O}$ and $\log k - \log C_{H^+}$ vs $-\log a_{H_2O}$. The slope value $\omega = 8.10 (\pm 0.42)$ which is greater than 3.3, so the reaction is bimolecular in nature. The slope (ω^*) is another parameter which is obtained by the plot between $\log k - \log C_{H^+}$ and $-\log a_{H_2O}$. The slope value is equal to $3.38 (\pm 0.49)$. The small curvature and positive slope (ω^*) also supports the bimolecular reaction path of hydrolysis (Figure not shown).

Table 2 Zucker-Hammett, Bunnett and Bunnett-Olsen plot data for the hydrolysis of mono-N-ethyl-*o*-toluidine phosphate

HCl (mol dm ⁻³)	log C _{H⁺}	$k \times 10^3$ (min ⁻¹)	$3+\log k$	$3+\log k - \log$ C _{H⁺}	$-H_0$	$3+\log k$ + H_0	$-\log C_{H^+} +$ H_0	$-\log a_{H_2O}$
1.0	0.00	21.10	1.32	1.32	0.20	1.12	0.20	0.02
1.5	0.18	31.76	1.50	1.32	0.47	1.03	0.29	0.03
2.0	0.30	38.14	1.58	1.28	0.69	0.89	0.39	0.04
2.5	0.40	52.19	1.72	1.32	0.87	0.85	0.47	0.05
3.0	0.48	66.22	1.82	1.34	1.05	0.77	0.57	0.07
3.5	0.54	77.67	1.89	1.35	1.23	0.66	0.69	0.09
4.0	0.60	96.76	1.99	1.39	1.40	0.59	0.80	0.11
4.5	0.65	82.42	1.92	1.27	1.58	0.34	0.93	0.13
5.0	0.70	63.67	1.80	1.1	1.76	0.04	1.06	0.16
6.0	0.78	43.58	1.64	0.86	2.12	-0.48	1.34	0.21
7.0	0.84	19.91	1.30	0.46	2.53	-1.23	1.69	0.28

Bunnett and Olsen [15] suggested a new parameter i.e. (ϕ) which is a slope of plot between $\log k + H_0$ and $-\log C_{H^+} + H_0$ (Figure not shown). This parameter was used to signify dependence of rate of hydrolysis on water activity. The value of the slope (ϕ) is $1.05 (\pm 0.06)$, which is in favour of the fact that water activity is playing an important role in deciding the rate at higher acidic concentration, water is involved in slow step and behaves as a proton transfer agent too (Table 2). One or approximately one value of (ϕ) indicates dependence of rate on water activity and acid concentration.

Effect of solvent

Solvent effect has been studied using different percentage of dioxane-water mixture. Table 3 shows a significant rise in rates with increase in dioxane percentage. This may be due to better proton donating capacity of dioxane than the water. Effect of solvent on the rate of hydrolysis indicates the transition state in which the charge is dispersed. This is in accordance with Chanley's observation [16].

Table 3 Rate of the hydrolysis of mono-N-ethyl-*o*-toluidine phosphate in acidic media at 50°C

% of dioxane (v/v)	HCl (mol dm ⁻³)	$k \times 10^3$ (min ⁻¹)	HCl (mol dm ⁻³)	$k \times 10^3$ (min ⁻¹)
0.00		66.22		63.67
10.0		73.85		67.91
20.0	3.0	77.76	5.0	74.67
30.0		83.68		81.47
40.0		89.90		85.64

Effect of temperature

For finding out the effect of temperature on the rate of hydrolysis of mono-N-ethyl-*o*-toluidine phosphate, a series of kinetic runs have been designed at 5.0 mol dm⁻³ HCl, using different temperatures. Arrhenius parameters [17] have been determined for the hydrolysis at 5.0 mol dm⁻³ HCl (Table 4). The magnitude of the Arrhenius parameters falls in the range of bimolecular reaction.

Table 4 Arrhenius parameters for hydrolysis of mono-N-ethyl-*o*-toluidine phosphate at 50°C

HCl (mol dm ⁻³)	Slope	Parameters		
		E (kcal mol ⁻¹)	A (sec ⁻¹)	$-\Delta S^\ddagger$ (e. u.)
5.0	-0.030	13.73	1.23×10^8	23.70

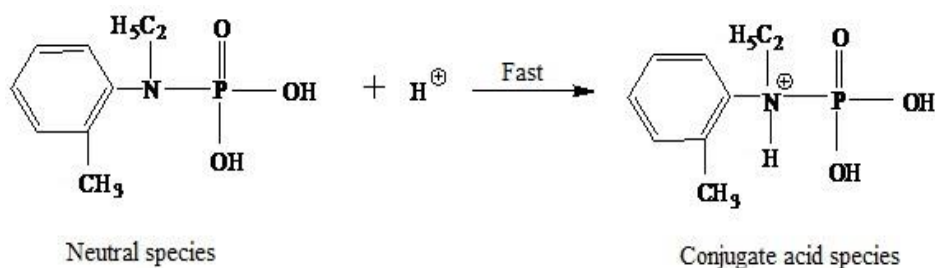
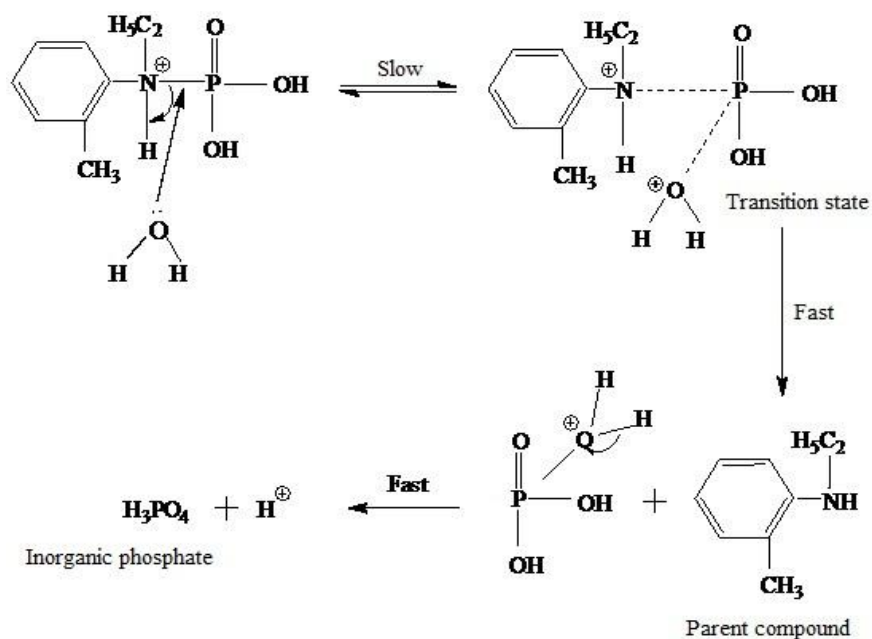
A comparative kinetic study of the acid-catalyzed hydrolysis of mono-N-ethyl-*o*-toluidine phosphate with other monoesters, which also give a linear relation between rates and hydrogen ion concentration in moderately acid solution and resemble simple esters in behavior, helps in presuming a bimolecular nucleophilic attack of water involving P-N bond fission (Table 5). Thus, the acid-catalyzed hydrolysis of mono-N-ethyl-*o*-toluidine phosphate ester involves the bimolecular attack of water on phosphorous of conjugate acid species formed by fast pre-equilibrium proton transfer.

Table 5 Comparative kinetic rate data for the hydrolysis of some phosphate monoesters via their conjugate acid species

S. No.	Phosphate Monoester	HCl (mol dm ⁻³)	E (kcal mol ⁻¹)	-ΔS [‡] (e.u.)	Bond Fission	Molecularity
1.	<i>p</i> -nitro aniline	3.0	15.25	9.5	P-N	2
2.	2-methyl-5-nitroaniline	4.0	13.70	22.90	P-N	2
3.	<i>p</i> -methoxy aniline	4.0	12.77	31.46	P-N	2
4.	<i>p</i> -butyl aniline	5.0	10.25	47.81	P-N	2
5.	2-chloro-5-nitroaniline	4.0	13.54	32.65	P-N	2
6.	N-ethyl- <i>o</i> -toluidine	5.0	13.73	23.7	P-N	Present work

Mechanism of hydrolysis

(a) Formation of conjugate acid species by fast pre-equilibrium proton transfer

(b) Bimolecular nucleophilic attack of water on phosphorous via conjugate acid species S_N²

Mechanism of hydrolysis

Conclusions

Mono-N-ethyl-*o*-toluidine phosphate ester in 0.1-7.0 mol dm⁻³ HCl has been found to hydrolyze via neutral and conjugate acid species. The acid-catalyzed hydrolysis is subjected to the positive effect of the ionic strength. The bimolecular nature of hydrolysis was supported by different parameters such as Arrhenius, Bunnett, Bunnett-Olsen, Hammett, Zucker-Hammett hypothesis. The bimolecular attack of water on phosphate ester under investigation is taken to proceed via P-N bond fission. Isokinetic relationship plots among the same type of ester support this particular rupture. Based upon this, complete hydrolytic mechanisms have been suggested.

Acknowledgements

The authors are thankful to Head, School of Studies in Chemistry, Pt. Ravishankar Shukla University, Raipur (C.G.) for kind support and providing research facilities.

References

- [1] Schultz C, Bioorganic & Medicinal Chemistry, 2003, 11, 885-898.
- [2] Bowler MW, Cliff MJ, Waltho JP, Blackburn GM, New J Chem, 2010, 34, 784.
- [3] Yadav H, Bhoite SA, Inter J of Sci Research, 2014, 3(6), 63-65.
- [4] Salamova A, Ma Y, Venier M, Hites RA, Environ Sci Technol Lett, 2014, 1, 8-14.
- [5] Ali RM, Hameed AS, Ameer AA, National Journal of Chemistry, 2005, 19, 426-439.
- [6] Veen IV, Boer J, Chemosphere, 2012, 10, 1119-1153.
- [7] Oelkers EH, Jones EV, Elements, 2008, 4, 83.
- [8] Cavalier J, Bull Soc Chem (France), 1895, 13, 885.
- [9] Allen RJL, J Biochem, 1940, 34, 858.
- [10] Lefler JE, Garunwald, The rates and equilibria of organic reactions, John Wiley and Sons Inc, New York, 1963, 286.
- [11] Barnard PWC, Bunton CA, Kellermann D, Mhala MM, Silver B, Vernon CA, Welch VA, J Chem Soc (B), 1968, 229.
- [12] Zucker L, Hammett LP, J Am Chem Soc, 1939, 61, 2791.
- [13] Hammett LP, Physical organic chemistry, McGraw-Hill, London, 1940, 335.
- [14] Bunnett JF, J Am Chem Soc, 1961, 83, 4956.
- [15] Bunnett JF, Olsen FF, Canadian J Chem, 1966, 44, 1917.
- [16] Chanly JD, Feageson EJ, J Am Chem Soc, 1958, 80, 2686.
- [17] Arrhenius S, J Phy Chem, 1889, 4, 226.

© 2014, by the Authors. The articles published from this journal are distributed to the public under "Creative Commons Attribution License" (<http://creativecommons.org/licenses/by/3.0/>). Therefore, upon proper citation of the original work, all the articles can be used without any restriction or can be distributed in any medium in any form.

Publication History

Received 28th July 2014
Revised 11th Aug 2014
Accepted 18th Aug 2014
Online 30th Aug 2014