

## EFFECT OF SUBSTITUTION AND MEDIUM ON BASIC HYDROLYSIS OF AMIDOPHOSPHORIC ACIDS DIPHENYL ESTERS

František KAŠPÁREK and Jiří MOLLIN

*Department of Inorganic Chemistry and  
Department of Physical Chemistry,  
Palacký University, 771 47 Olomouc*

Received September 26th, 1977

*Dedicated to Professor A. Okáč, Corresponding member of the Czechoslovak Academy of Sciences, on the occasion of his 75th birthday.*

The pH profiles of the reaction rate constant logarithms were measured in water-ethanol media of different ratios of the components. The activation parameters of the hydrolytic reaction were determined for all the substances studied and the products of hydrolysis of anilidophosphoric acid diphenyl ester in 50% (w/w) ethanol were identified. The rate constants of the basic hydrolysis of anilido- and N-methylamidophosphoric acid substituted diphenyl esters obey the Hammett equation. All experimental results confirm unequivocally the  $S_N2$  mechanism of the reaction in question.

The  $S_N2$  mechanism has been established for the base-catalyzed hydrolysis of N-alkyl-amido- and substituted anilidophosphoric acids diphenyl esters based on the activation entropies and the plateau on the kinetic conversion curves<sup>1</sup>. For N-alkylamidophosphoric acids this conclusion has been confirmed by the positive  $\rho^*$  constant value of the Taft equation, for substituted anilidophosphoric acids, however, a value of the Hammett  $\rho$  constant approaching zero has been found, which is seldom encountered in the literature. For this reason we focused our attention on N-methylamidophosphoric and anilidophosphoric acids substituted phenyl esters in order to establish the effects which cause the zero value of the  $\rho$  constant of the Hammett equation for the reaction in question.

### EXPERIMENTAL

N-Methylamido- and anilidophosphoric acids diphenyl esters were prepared by the common aminolysis of chlorides of the phosphoric acid substituted diphenyl ester in an inert solvent<sup>2</sup>. N-Methylamidophosphoric acid di-(*p*-methoxyphenyl) ester (*I*), di-*p*-tolyl ester (*II*), di-*m*-tolyl ester (*III*), diphenyl ester<sup>3</sup> (*IV*), di-*p*-chlorophenyl ester (*V*), and di-*m*-nitrophenyl ester (*VI*) were prepared. Anilidophosphoric acid di-*p*-methoxyphenyl ester (*VII*), di-*p*-tolyl ester<sup>4</sup> (*VIII*), di-*m*-tolyl ester<sup>4</sup> (*IX*), diphenyl ester<sup>3</sup> (*X*), di-*m*-methoxyphenyl ester (*XI*), di-*p*-chlorophenyl ester (*XII*), and di-*m*-nitrophenyl ester (*XIII*) were prepared as well. The results of analyses of newly prepared substances, their melting points, and the solvents employed are given in Table I.

A saturated solution of *IV* in chloroform was diluted with equal volume of chloroform or 1,4-dioxane for the measurements of the infrared spectra. The spectra were run on an instrument UR 10 (Zeiss, Jena) in the region of the N—H bond stretching vibrations.

The reaction products of the base-catalyzed hydrolysis of *X* were identified and determined by combining paper chromatography and photometry. After completed hydrolysis of *X* in 0.1M-NaOH in 50% (w/w) ethanol, the solution was chromatographed using the solvent isopropyl alcohol-isobutyl alcohol-water-concentrated NH<sub>3</sub> 20 : 60 : 19 : 1 (Whatman No 4). As the testing substances served the sodium salts of anilidophosphoric acid phenyl ester<sup>5</sup> (*XIV*) and of anilidophosphoric acid ethyl ester (*XV*), obtained by basic hydrolysis of the corresponding diethyl ester<sup>6</sup>. After elution the spots were detected<sup>7</sup>, cut out, and ashed<sup>8</sup>. The content of phosphorus was determined according to<sup>9</sup>.

The pH was measured by using a hydrogen electrode against a silver chloride (in water-ethanol mixtures) or calomel (in water) electrode<sup>10</sup>.

For the kinetic measurements the technique described previously<sup>1</sup> was used.  $3 \cdot 10^{-5}$  M to  $2 \cdot 10^{-4}$  M solutions of *I* to *XIII* in glycinate buffers were prepared and their spectra measured both immediately and after the completed hydrolysis. From the difference between the spectra, the wavelength was chosen for the kinetic measurements. The glycinate buffer was obtained

TABLE I  
Survey of the Newly Prepared Compounds

Substance	M.p., °C solvent	Formula m.wt.	Calculated/Found, %			
			C	H	N	P
<i>I</i>	101 ethanol	C <sub>15</sub> H <sub>18</sub> NO <sub>5</sub> P 323.3	55.73	5.61	4.33	9.58
			56.11	5.71	4.18	9.68
<i>II</i>	102—104 ethanol	C <sub>15</sub> H <sub>18</sub> NO <sub>3</sub> P 291.3	61.85	6.23	4.81	10.63
			61.97	6.35	4.75	10.92
<i>III</i>	45—47 ether/pentane	C <sub>15</sub> H <sub>18</sub> NO <sub>3</sub> P 291.3	61.85	6.23	4.81	10.63
			62.99	6.36	4.44	10.02
<i>V</i>	90—91 ethanol	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> NO <sub>3</sub> P 332.1	47.00	3.64	4.22	
			47.47	3.53	3.91	
<i>VI</i>	121 ethanol	C <sub>13</sub> H <sub>12</sub> N <sub>3</sub> O <sub>7</sub> P 353.2	44.21	3.42	11.90	
			44.20	3.45	11.67	
<i>VII</i>	127—129 ethanol	C <sub>20</sub> H <sub>20</sub> NO <sub>5</sub> P 385.3	62.34	5.23	3.63	8.04
			62.14	5.36	3.43	8.33
<i>XI</i>	114—115 ethanol	C <sub>20</sub> H <sub>20</sub> NO <sub>5</sub> P 385.3	62.34	5.23	3.63	8.04
			62.09	5.37	3.52	8.17
<i>XII</i>	163 acetone	C <sub>18</sub> H <sub>14</sub> Cl <sub>2</sub> NO <sub>3</sub> P 394.2	54.85	3.58	3.55	7.86
			55.02	3.64	2.83	7.54
<i>XIII</i>	154—156 ethanol	C <sub>18</sub> H <sub>14</sub> N <sub>3</sub> O <sub>7</sub> P 415.3	52.06	3.40	10.12	7.46
			51.24	3.29	9.61	7.41

by mixing 0.1M glycine and 0.1M-NaOH solutions (both *p.a.*, Lachema) in the same solvent — 50, 30, or 10% (w/w) ethanol and water. The thermostat, spectrophotometer, and calculation method used have been described previously<sup>1</sup>. The rate constant errors are less than 5%. The activation parameters were calculated from five rate constant values measured at 30, 35, 40, 45, and 50°C. The temperature dependences of the rate constants of all the compounds were of the Arrhenius form. For the investigation of the dependence of the rate constant on the ionic strength, the latter was adjusted with sodium perchlorate (*p.a.*, Lachema).

The dissociation constants of the substituted anilidophosphoric acids phenyl esters were determined photometrically<sup>1</sup>.

## RESULTS AND DISCUSSION

The IR spectra of chloroform solutions of *IV* exhibit a sharp absorption band of the N—H stretching vibration at 3440 cm<sup>-1</sup>. In the chloroform–dioxane mixed solvent this band is shifted to 3300 cm<sup>-1</sup> and becomes less sharp. Similarly as with other amides<sup>11</sup>, this shift and broadening of the NH absorption band of N-methylamidophosphoric acid phenyl ester indicates the formation of a hydrogen bond between the N—H group and the dioxane oxygen atom as the electron donor; thus the spectra confirm the assumed<sup>1</sup> solute–solvent bridges.

During the identification of the solvolytic products of *X*, a measurable amount of *XV* was found in the products in addition to *XIV*; its production is less than 3% of the total of the amidophosphate. This experiment rules out the E<sub>1</sub>cB mechanism of the hydrolytic reaction, which would afford a mixture of *XIV* and *XV* approximately 1 : 1, owing to the high reactivity of the possible intermediate product with trivalent phosphorus<sup>12</sup>. In the base-catalyzed solvolysis of carboxylic acid phenyl esters in a water–ethanol mixed solvent, the hydrolysis predominates over the alcoholysis. This reaction proceeds undoubtedly through the S<sub>N</sub>2 mechanism in the reaction rate-determining step<sup>13</sup>. If the same relation of the reactivities of water and alcohol is assumed to the two groups of substances, the formation of the acid confirms the S<sub>N</sub>2 mechanism also for the solvolysis of the amidophosphoric acids diesters.

The plateau at the beginning of the conversion curves of N-alkylamidophosphoric acids, found previously and interpreted in terms of the formation of a relatively stable intermediate product involving pentavalent phosphorus<sup>1</sup>, was observed with all substances examined in this work as well. It was the more pronounced, the lower was the pH of the solution. This effect leads again to the concept of a relatively stable intermediate product with pentavalent phosphorus and prefers the S<sub>N</sub>2 reaction mechanism for the whole series of the compounds. This conclusion is in accordance with the results of analyses of the reaction products.

The photometrically determined pK values of the phenyl anilidophosphates examined, measured in 50% (w/w) ethanol at room temperature ( $\lambda_{\max}$  250 nm), are as follows: *VII* 13.9, *VIII* 13.6, *IX* 14.0, *X* 13.5, *XI* 13.15, *XII* 12.4, and *XIII* 11.15. Except for *IX* these values obey the Hammett equation with  $\rho = +2.81$ . This  $\rho$  con-

TABLE II

Rate Constants of N-Methylamido- and Anilidophosphoric Acids Substituted Diphenyl Esters I—XIII in 50% (w/w) Ethanol

pH $k_{\text{exp}} \cdot 10^5, \text{s}^{-1}$		pH $k_{\text{exp}} \cdot 10^5, \text{s}^{-1}$		pH $k_{\text{exp}} \cdot 10^5, \text{s}^{-1}$	
<i>I</i> , 309.5 nm		<i>II</i> , 239.0 nm		<i>III</i> , 240.5 nm	
11.41 1.83		11.78 6.83		11.91 7.88	
11.78 4.05		11.91 7.71		12.05 8.11	
11.91 5.48		12.05 10.67		12.11 9.36	
12.11 5.70		12.34 19.48		12.34 16.98	
12.34 15.02		12.70 46.04		12.45 29.79	
		12.85 73.48		12.85 64.69	
<i>IV</i> , 236.5 nm		<i>V</i> , 246.0 nm		<i>VI</i> , 227.4 nm	
11.42 6.30		9.98 1.81		9.98 16.73	
11.54 7.09		10.49 3.98		10.49 46.67	
11.61 9.44		11.00 13.14		10.62 77.20	
11.77 10.09		11.38 20.80		10.79 103.50	
11.91 14.25		11.59 29.00		10.89 120.10	
11.98 15.76		11.89 49.50		10.96 162.40	
12.13 20.89		11.99 59.20			
12.30 22.45					
12.52 38.72					
<i>VII</i> , 309.5 nm		<i>VIII</i> , 297.5 nm		<i>IX</i> , 287.5 nm	
11.62 0.481		11.49 1.05		10.96 0.447	
11.98 0.982		11.62 1.19		11.49 0.949	
12.23 1.78		11.98 2.13		11.62 1.31	
12.50 2.34		12.23 2.88		11.98 2.43	
12.70 3.46		12.50 3.30		12.23 3.23	
12.99 4.51		12.70 5.96		12.50 4.06	
		12.99 9.17		12.70 6.81	
				12.99 11.80	
<i>X</i> , 289.5 nm		<i>XI</i> , 287.5 nm		<i>XII</i> , 302.0 nm	
10.96 0.932		10.96 0.965		10.96 5.32	
11.49 1.80		11.49 2.41		11.49 8.76	
11.62 2.28		11.62 3.12		11.62 10.00	
11.98 4.31		11.98 5.14		12.23 22.40	
12.23 4.78		12.23 7.77		12.50 25.00	
12.50 7.17		12.50 9.26		12.70 30.80	
12.70 10.80		12.70 13.20			
12.99 17.30				<i>XIII</i> , 230.2 nm	
				9.98 7.25	
				10.62 22.20	
				10.79 29.50	
				10.96 43.10	
				11.49 84.60	

stant indicates a very good transmission of the inductive effects *via* the phosphorus atom<sup>14</sup>. N-Methylamidophosphoric acids esters possess  $pK$  values greater than 14, their acid-base properties were therefore not further studied.

Regarding the solubilities of the substances under study, the pH profiles of the rate constant logarithms were measured in 50% (w/w) ethanol; the results are given in Table II. The rate constants were calculated from Eq. (2) of the paper<sup>1</sup>. The agreement between this equation and the experiment justifies the conclusion that the reaction is in all instances kinetically 1st order with respect to the concentration of the N-substituted amidophosphoric acid diester.

In the paper<sup>1</sup> the hydrolysis of the substance studied was formulated as the reaction of a nondissociated molecule of the amidophosphoric acid diester with an  $\text{OH}^-$  ion. This concept is supported by the dependence of the rate constant on the ionic strength of the solution ( $8 \cdot 10^{-5}\text{M}$  solution of *IV* in  $5 \cdot 10^{-3}\text{M}$ -NaOH in 50% (w/w) ethanol at 45°C): for the ionic strengths 0.005, 0.1, 0.25, 0.50, 0.75, 1.00, and 2.00, the rate constants are 2.27, 2.04, 1.90, 1.90, 2.04, 1.89, and  $1.79 \cdot 10^{-4} \text{ s}^{-1}$ , respectively.

Since the hydrolysis of the anilidophosphoric acids diesters proceeds in a region close to their  $pK$  (Table II), the experimental rate constants  $k_{\text{exp}}$  were recalculated to the  $k'$  values according to Eq. (14) of ref.<sup>1</sup>. The slopes of the plots of  $\log k'$  versus pH approached unity. In the case of N-methylamidophosphoric acid diesters, the kinetically examined region was sufficiently far from the  $pK$ , for these compounds the  $k_{\text{exp}}$  values were therefore not recalculated and the plot of their logarithms versus pH displayed a slope near 0.75. This shows that the hydrolytic reaction is kinetically of the first order with respect to the  $\text{OH}^-$  ion concentration for the whole series studied. For anilidophosphoric acid diesters the dependence of the logarithm of the rate constant  $k'$  on the substitution was examined in solutions pH 11.62. The values obeyed the Hammett equation with  $\rho = 3.01$ . The analogous dependence of  $\log k_{\text{exp}}$  for N-methylamidophosphoric acid diesters at pH 11.91 led to the  $\rho$  value of 2.47. The rate constants of the *m*-nitro derivatives were obtained by extrapolation in both cases. The positive  $\rho$  value in the two series again favours the concept of the  $S_{\text{N}}2$  mechanism of the reaction studied. For the base-catalyzed hydrolysis of substituted benzoic acid phenyl esters, the  $\rho$  constant was found<sup>13</sup> to be 1.7. From a comparison of these values it follows that the substituent inductive effects manifest themselves very markedly during a nucleophilic addition on the phosphorus atom. It is interesting to compare this fact with the previously established<sup>1</sup> virtually zero  $\rho$  constant value of the hydrolytic reaction of substituted N-arylamidophosphoric acids diphenyl esters. Comparing the two effects we can conclude that the very low  $\rho$  constant value for the dependence of  $\log k'$  of basic hydrolysis of substituted anilidophosphoric acids diphenyl esters on the substituent  $\sigma$  constant is due to the low transmission of the inductive effects *via* the nitrogen atom. This is in accordance with the recent works where the low transmission of the inductive and mesomeric effects through the nitrogen atom has been observed during studies of equilibria<sup>15-17</sup> as well as kinetics<sup>18</sup>.

In conformity with the positive value of the  $\rho$  constant of the Hammett equation for the dependence of the rate constant logarithm on the substitution and with the concept of an intermediate product containing pentavalent phosphorus were also the reaction activation entropies, shown along with the activation enthalpies in Table III. Their negative values lie in a range, which is regarded as characteristic

TABLE III

Activation Enthalpies ( $\text{kJ mol}^{-1}$ ) and Activation Entropies ( $\text{J mol}^{-1} \text{K}^{-1}$ ) of Basic Hydrolysis of N-Methylamido- and Anilidophosphoric Acids Substituted Diphenyl Esters in 50% (w/w) Ethanol at 298.14 K and pH 12.11 or 12.70

Substance	$\Delta H^\ddagger$	$\Delta S^\ddagger$	Substance	$\Delta H^\ddagger$	$\Delta S^\ddagger$
<i>I</i>	61.2	-134.4	<i>VII</i>	64.2	-129.4
<i>II</i>	61.4	-129.1	<i>VIII</i>	71.8	-100.9
<i>III</i>	48.5	-170.6	<i>IX</i>	70.7	-102.6
<i>IV</i>	52.5	-151.0	<i>X</i>	75.6	-83.1
<i>V</i>	43.3	-168.3	<i>XI</i>	65.5	-113.7
			<i>XII</i>	59.3	-125.8

TABLE IV

Rate Constants of Hydrolysis of N-Methylamidophosphoric Acid Diphenyl Ester at 45°C

pH	$k_{\text{exp}} \cdot 10^5, \text{s}^{-1}$	pH	$k_{\text{exp}} \cdot 10^5, \text{s}^{-1}$	pH	$k_{\text{exp}} \cdot 10^5, \text{s}^{-1}$
50% (w/w) ethanol		30% (w/w) ethanol		10% (w/w) ethanol	
11.42	6.30	11.25	6.61	10.68	7.19
11.54	7.09	11.53	10.92	10.87	9.67
11.61	9.44	11.90	15.70	11.27	21.80
11.77	10.09	12.00	21.21	11.54	38.65
11.91	14.25	12.24	43.61	11.88	95.12
11.98	15.76	12.37	52.61	12.03	119.9
12.13	20.89				
12.30	22.45			0% (w/w) ethanol	
12.52	38.72			10.68	10.84
				10.96	22.28
				11.20	28.44
				11.32	43.51
				11.42	49.27
				11.68	75.98

of bimolecular reactions in the reaction rate-determining step<sup>19</sup>. The activation entropies given in Table III are calculated from the experimental first order rate constants, whereas the  $\Delta S^\ddagger$  values reported in the paper<sup>19</sup> have been calculated for second order reactions. With regard to the high pH value used for the measurement and to the region of values where the reaction can be considered as bimolecular the difference between the two kinds of values is insignificant.

The dependence of the rate constant on the solvent composition has been studied previously<sup>1</sup>. This dependence was now studied in detail for *IV* owing to its solubility, and the results are given in Table IV. In all solvents the dependence of  $\log k_{\text{exp}}$  on pH was linear with a slope near 0.75. The results of the previous work<sup>1</sup> obtained in 10% (w/w) ethanol seem to involve experimental error. The rate constants found in various solvents at pH  $\sim$  11.5 show that the rate of the hydrolytic reaction rises with increasing concentration of water, analogously as for carboxylic acid esters<sup>13,20,21</sup>.

The found activation entropies, the  $\rho$  constant of the Hammett equation for the dependence of  $\log k'$  of the hydrolytic reaction on the substitution, the plateaus on the conversion curves as well as the reaction products identified which are analogous to the products of base-catalyzed hydrolysis of carboxylic acid phenyl esters, confirm the previously suggested concept of the  $S_N2$  mechanism of the reaction under study in the reaction rate-determining step. Neither in the present nor in the previous<sup>1</sup> work was found any indication that contradicts this conclusion; we take therefore the problem of the molecularity of the reaction for uniquely solved.

#### REFERENCES

1. Mollin J., Veverka F., Kašpárek F.: This Journal 41, 3245 (1976).
2. Houben-Weyl: *Methoden der Organischen Chemie*, Vol. XIII2. Sasse K.: *Organische Phosphorverbindungen*, p. 419. G. Thieme Verlag, Stuttgart 1964.
3. Audrieth L. F., Toy A. D. F.: J. Amer. Chem. Soc. 64, 1337 (1942).
4. Autenrieth W., Geyer A.: Ber. Deut. Chem. Ges. 41, 146 (1908).
5. Kašpárek F.: Acta Univ. Palacki. Olomuc., Fac. Rerum Nat. 45, 23 (1974).
6. Atherton F. R., Todd A. R.: J. Chem. Soc. 1947, 674.
7. Hanes C. S., Isherwood F. A., Nature (London) 164, 1107 (1949).
8. Bennewitz R.: *Mikrochim. Acta* 1963, 1097.
9. Rössel T., Kieslich H.: Fresenius' Z. Anal. Chem. 225, 391 (1967).
10. Mollin J.: This Journal 40, 2266 (1975).
11. Walter W., Steffen M.: Justus Liebigs Ann. Chem. 712, 53 (1968).
12. Hudson R. F.: *Structure and Mechanism in Organo-Phosphorus Chemistry* (Russ.), p. 11. Mir, Moscow 1967.
13. Mollin J., Baisa A. A.: This Journal 43, 304 (1978).
14. Newman M. S.: *Steric Effects in Organic Chemistry* (Russian translation), p. 573. Izd. Inostr. Lit., Moscow 1960.
15. Exner O., Simon W.: This Journal 30, 4078 (1965).
16. Dutt N. K., Seshadri T.: Bull. Chem. Soc. Jap. 40, 2280 (1967).

17. Manole S. F., Filippov M. P., Barba N. A.: *Zh. Org. Khim.* 7, 2452 (1971).
18. Witiak D. T., Chin T.-F., Lach J. L.: *J. Org. Chem.* 30, 3721 (1965).
19. Schaleger L. L., Long F. A.: *Advan. Phys. Org. Chem.* 1, 1 (1963).
20. Tommila E., Hietala S.: *Acta Chem. Scand.* 8, 257 (1954).
21. Anantakrishanan S. V.: *Indian J. Chem.* 3, 336 (1965).

Translated by P. Adámek.