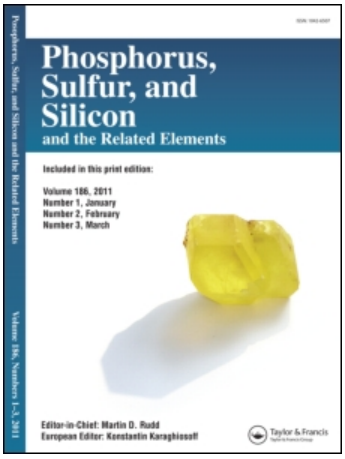

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Acid-Catalyzed Cleavage Of 2-Pyridyl and 4-Pyridyl Derivatives Of Aminomethylphosphonic Acid. Kinetic And Chemical Arguments For A Mechanism With A-S_E2 Character

Bogdan Boduszek[a]; Rafał Latajka[a]; Wojciech Leśniak[b]
[a] Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroctaw University of Technology, Poland [b] Faculty of Chemistry, University of Wroctaw, Poland

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ACID-CATALYZED CLEAVAGE OF 2-PYRIDYL AND 4-PYRIDYL DERIVATIVES OF AMINOMETHYLPHOSPHONIC ACID. KINETIC AND CHEMICAL ARGUMENTS FOR A MECHANISM WITH A-S_E2 CHARACTER

BOGDAN BODUSZEK[a*], RAFAŁ LATAJKA[a*] and WOJCIECH LEŚNIAK[b]

[a]*Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, 50–370 Wrocław, Poland, and* [b]*Faculty of Chemistry, University of Wrocław, 50–383 Wrocław, Poland*

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Studies of the acid-catalyzed cleavage of 2-pyridyl and 4-pyridyl(amino)methylphosphonic acids demonstrate that protonation has a profound effect on the cleavage of C-P bonds. In H_2SO_4, and other strong mineral acids the cleavage of aminophosphonic acids **1** and **4** exhibits a kinetic depedence on Zucker-Hammett acidity function (h_o), with rate law, $v = k[phosphonate]\cdot h_o$, and also fulfil the Bunnett approach on acidity function. The measured solvent isotope effect k_H/k_D is small, and varied from 1.46 for **1b** to 1.18 for **4b**. The isotope effect shows that protons are involved on the rate-determining step of the cleavage. All of this evidence indicates that the cleavage of **1** or **4** shows A-S_E2 character substitution reaction. Calculated activation parameters and some chemical experiments indicate that the protonated phosphonate molecule is split by a dissociative mechanism, combined with formation of a positive-charged phosphorus moiety.

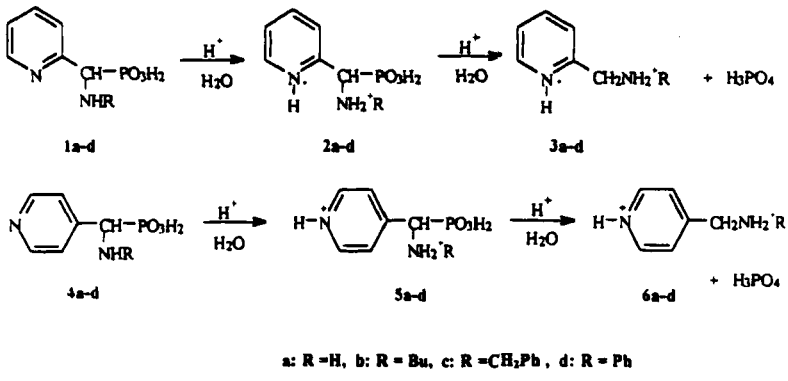
Keywords: Acidity; Catalysis; Cleavage reactions; Protonations; Phosphonates; Pyridines

INTRODUCTION

In 1996, we reported an unusual reaction of a cleavage of 2-pyridyl- and 4-pyridyl(amino)methylphosphonates in acidic conditions[1]. As a result

* E-mail: boduszek@kchf.ch.pwr.wroc.pl

of that cleavage, the corresponding pyridylmethylamines and phosphoric acid were formed. Such a cleavage of the 2-and 4-pyridyl derivatives of aminomethylphosphonic acid is illustrated below (Scheme 1).



SCHEME 1 Cleavage of 2- and 4-Pyridyl Derivatives of Aminomethylphosphonic Acid in Strong Mineral Acids

A replacement of the amino group by the hydroxy one in aminophosphonic acids **1** or **4** inhibits entirely the cleavage [1]. In turn, the parent 3-pyridyl derivatives of aminomethylphosphonic acid are stable in strong mineral acids and do not undergo such a cleavage [1]. And interestingly, all of the considered phosphonic acids **1** and **4** are stable in basic conditions.

In a previous paper [1] we proposed a mechanism of this cleavage, comprising a presumption of an elimination of a positively charged phosphorus species from the protonated aminophosphonate molecule.

Generally, there are postulated two types of substitution reactions at the phosphorus atom. The first one, an associative $S_N2(P)$ mechanism (with formation of a pentacoordinated intermediate), and the second one, a dissociative $S_N1(P)$ mechanism, assuming the formation of a highly reactive metaphosphate intermediate ($ROPO_2$). These two mechanisms are well documented in the literature [12,13,45].

In contrast to the mechanistic pathways mentioned above, the formation of a discrete positively charged tricoordinated phosphorus species, namely RR P^+=X (X= O, S), has remained the subject of controversy, despite of intensive studies in this field [3,4]. Nevertheless, formation of such a positive charged phosphorus species (a phosphacylium cation, X= O) is considered in some cases as the intermediate [5,6]. Similar structures are also

proposed as transition states [7–11] in reactions of hydrolysis of some organophosphorus compounds, such as phosphinyl amides or chlorides. However, it seems, that the strongest evidence for existence of the phosphacylium-type cations comes from mass spectroscopy studies of dialkylphosphinic acids and their esters [14, 15]and also phosphonates [25, 26]. In all these mass spectrometric investigations, various protonated metaphosphates were observed, namely, the protonated metaphosphoric acid ($H_2PO_3^+$) [25,26] or the phosphacylium ion ($R_2P^+{=}O$) [14].

In order to establish an acceptable mechanism for the cleavage of 2- or 4-pyridyl-(amino)methylphosphonates, we decided to perform some additional kinetic measurements on this reaction, which would provide rates, order of the reaction and activation parameters. Kinetic measurements were performed by using ^{31}P NMR and were limited to cleavage of the 2-pyridyl- (**1a-d**) and 4-pyridyl(amino)methylphosphonic acids (**4a-d**) [2]. This is because the dialkyl and diaryl esters derived from the phosphonic acids **1** and **4** are also cleaved in acidic conditions by the same way [1], but these reactions are more complex, due to some simultaneous parallel processes occurring in the time of treatment of the esters with mineral acids. During hydrolysis of the phosphonate ester, the corresponding phosphonic acid is formed and a simultaneous cleavage of the ester (or the formed phosphonic acid) occurs. The rates of these processes (hydrolysis and cleavage) are comparable. Therefore, in order to avoid an additional complication during kinetic measurements, we decided to limit the investigations to free phosphonic acids.

RESULTS

Kinetic measurements

Two representative compounds **1b** and **4b**, being N-butyl derivatives of the 2-pyridyl and 4-pyridyl(amino)methylphosphonic acids [2] were chosen for most kinetic experiments. Other derivatives (**1a,c,d** and **4a,c,d**) were additionally investigated, in order to compare the obtained rate constant (k_{obs}) for several substrates.

Kinetic measurements were made by ^{31}P NMR. Solutions of the corresponding pyridyl(amino)methylphosphonic acid, containing appropriate concentration of mineral acid were heated in NMR tubes at 95 °C, for

specified period of time and (after cooling) ^{31}P NMR spectra were recorded. Kinetic data were obtained from the spectra, on the basis of observed decrease with time in the concentration of the phosphonic acid and the simultaneous increase in the concentration of H_3PO_4 formed The concentrations were calculated from the integration values of individual phosphorus compounds.

Depedence of rate on acidity

The pseudo-first-order rate constants (k_{obs}) can be accurately determined from ^{31}P NMR spectra by plotting dependence of $log(a-x)$on time (where the "$a-x$" represents an actual concentration of the unreacted phosphonic acid). The data obtained are summarized in Table I. In Table I the literature values of the Zucker-Hammett acidity function (H_o)[16] corresponding to the concentrations of sulfuric and hydrochloric acids used are also given. In addition, there are also shown the literature values of the $log[a_{H2O}]$ [18] for aqueous solutions of acids. These data were used for analysis of the dependence of rate on acidity.

Table I showed that k_{obs} depended on the acid concentration. For lower concentrations of D_2SO_4 (or H_2SO_4) lying in the range of 0.2→1.0 mol·L^{-1}, the rates increase faster than could be expected from direct proportionality to the concentrations of acid (see data for **1b** and **4b**, Table 1, and Fig. 1). For higher concentrations of acid the rates increase more slowly. And, finally, for concentrations of acid exceeding 2.0 mol·L^{-1} (see data for **4b**, in D_2SO_4, Table I) the rates decrease gradually.

Comparison of the rates for the cleavage of 2-pyridyl derivatives (**1a-d**) with the rates determined for 4-pyridyl ones (**4a-d**) shows a remarkable difference. The 2-pyridyl derivatives undergo cleavage about five times faster than 4-pyridyl compounds.

Rates of cleavage for other phosphonic acids (**1a,c,d** and **4a,c,d**) differ considerably and depend on substituents on the amino group. The *N*-benzyl derivatives (**1c, 4c**) were cleaved approximately twice as fast as the corresponding *N*-butyl derivatives (**1b, 4b**). The slowest rates of cleavage were observed for *N*-phenyl derivatives (**1d, 4d**).

The observed rates for the cleavage of the individual compounds do not vary significally between various acids H_2SO_4, HCl, HBr) used at the same concentrations. Moreover, an addition of a large amount of NaBr to the hydrobromic acid decreases the rate of cleavage (see the run in HBr

solution, Table I). It indicates that the presence of a large excess of a strong nucleophile rather inhibits than accelerate the cleavage.

TABLE I Kinetics for the Acid-Catalyzed Cleavage of 2-Pyridyl(amino)methylphosphonic Acids **1a-d** and 4 Pyridyl(amino)methylphosphonic acids **4a-c** at 95°C

Compd.	*Solvent*	*Acid*	*Conc. of Acid mol·L^{-1}*	*$10^5 \cdot k_{obs}$ [a] s^{-1}*	*Ho* [b]	*log[a_{H2O}]* [c]
1b	H_2O	H_2SO_4	0.5	1.9	0.13	–0.008
			1.0	4.6	–0.26	–0.018
			1.5	6.3	–0.56	–0.030
			2.0	7.2	–0.84	–0.043
	D_2O	D_2SO_4	0.37	0.9	[d]0.28	
			0.5	1.3	0.13	
			1.0	3.5	–0.26	
			2.0	4.9	–0.84	
	H_2O	HCl	1.0	4.9	–0.20	–0.017
			2.0	8.5	–0.69	–0.039
	H_2O	HBr	1.0	3.9	–0.20	
			2.0	7.8	–0.71	
			[e]2.0(+ NaBr)	5.2		
1a	H_2O	H_2SO_4	1.0	2.1	–0.26	–0.018
1c	H_2O	H_2SO_4	1.0	9.7	–0.26	–0.018
1d	H_2O	H_2SO_4	1.0	0.5	–0.26	–0.018
4b	H_2O	H_2SO_4	0.5	0.58	0.13	–0.008
			1.0	1.10	–0.26	–0.018
			1.5	1.15	–0.56	–0.030
			2.0	1.20	–0.84	–0.043
	D_2O	D_2SO_4	0.2	0.18	[d]0.57	
			0.4	0.46	0.24	
			0.5	0.49	0.13	
			1.0	0.97	–0.26	
			2.0	1.18	–0.84	
			3.0	1.10	–1.38	
			4.0	0.83	–1.85	
			5.0	0.73	–2.28	
	H_2O	HCl	1.0	1.05	–0.20	–0.017
			2.0	1.43	–0.69	–0.039
	H_2O	HBr	1.0	0.80	–0.20	
			2.0	1.11	–0.71	
4a	H_2O	H_2SO_4	1.0	0.37	–0.26	–0.018

Compd.	*Solvent*	*Acid*	*Conc. of Acid mol·L^{-1}*	*$10^5 \cdot k_{obs}$ [a] s^{-1}*	*Ho* [b]	*log[a_{H2O}]* [c]
4c	H_2O	H_2SO_4	1.0	1.80	–0.26	–0.018
4d	H_2O	H_2SO_4	1.0	0.31 [f]	–0.26	–0.018

a. Rates reproducible to ± 5%.
b. Values of H_o for H_2SO_4 and HCl are given by Paul and Long [6].
c. Values of $log[a_{H2O}]$ are given by Bunnett [18].
d. Values of H_o for H_2SO_4 and D_2SO_4, likewise for other strong acids are practically equal at the same concentrations [16].
e. The kinetic run was measured in a solution composed with 2.0 mol·L^{-1} HBr and 4.0 mol·L^{-1} NaBr.
f. This value is uncertain, due to non-linear kinetics.

The slopes for a linear dependence are: 1.09 for **1b** and 0.86 for **4b**. There is also a considerable deviation from linear dependence of log k_{obs} on H_o, for concentrations of sulfuric acid exceeding 1.0 mol·L^{-1}.

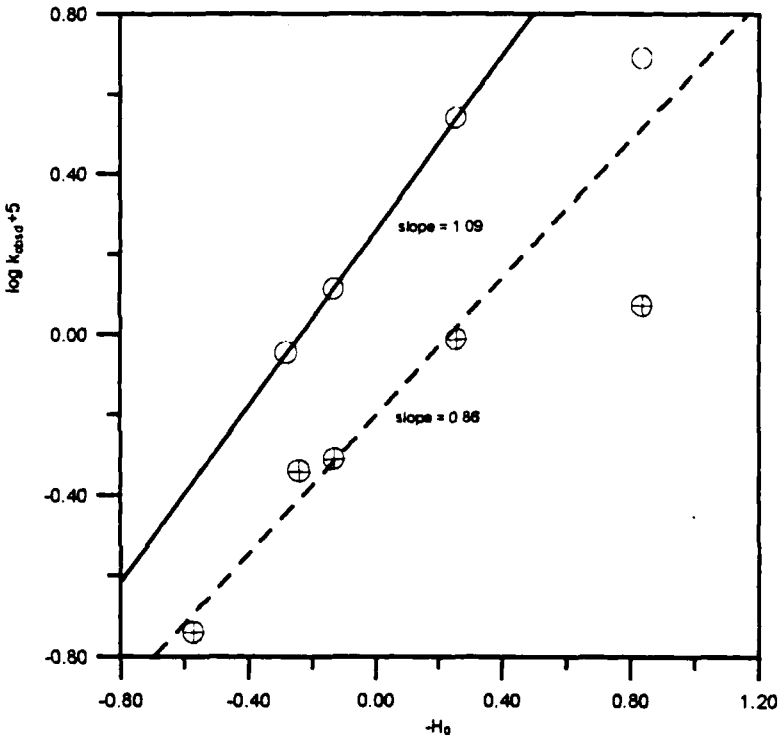


FIGURE 1 Dependence of $log[10^5 k_{obs}]$ on $-H_o$ in D_2SO_4 for the Cleavage of **1b** (o) and **4b** (+) The dependence of log k_{obs} on H_o for the cleavage of **1b**and **4b** is displayed in Figure 1

Because the plot of k_{obs} on H_o is not linear for the higher concentrations of sulfuric acid, the Bunnett approaches [18–21] to solvation of acid-catalyzed reactions were applied for analysis of our data. An example of the Bunnett method, examining the dependence of log k_{obs} $+H_o$ on activity of water in aqueous solutions of H_2SO_4, is presented below (Figure 2).

Contrary to the H_o function, the plot of *log* k_{obs} $+H_o$ on *log* a_{H2O}demonstrates a good linearity for higher concentrations of sulfuric acid, namely those exceeding 1.0 mol·L^{-1}. The slopes obtained "*w*" were 14.4 for **1b** and 19.1 for **4b**. The values of *w* are surprisingly high, considerably higher than the typical values of *w* reported by Bunnett [18]. These data would suggest a different mechanism of the cleavage occurring in high concentrations of sulfuric acid.

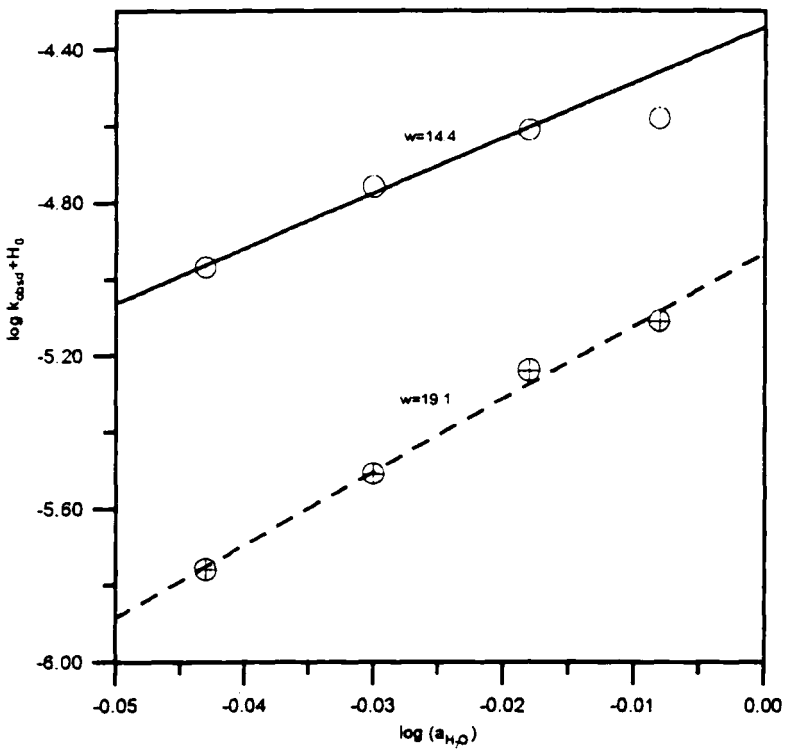


FIGURE 2 Dependence of log k_{obs} + $H_o$on $log[a_{H2O}]$ in H_2SO_4Solutions for the Cleavage of **1b** (o) and **4b** (+)

Solvent isotope effects k_H/k_D

Solvent deuterium isotope effects were evaluated in sulfuric acid, for two concentrations of H_2SO_4 and D_2SO_4, respectively. The values of k_H/k_D are summarized in Table II. The k_H/k_D is generally higher for **1b** than for **4b**. Interestingly, the k_H/k_D for **4b** approaches unity in more concentrated sulfuric acid.

TABLE II Solvent Deuterium Isotope Effect for the Cleavage of **1b** and **4b** in Sulfuric Acid

Compd.	$[H_2SO_4]or[D_2SO_4]$	$10^5 k_{obs}$, s^{-1}		
	$mol \cdot L^{-1}$	H_2O	D_2O	k_H/k_D
1b	0.5	1.9	1.3	1.46
1b	2.0	7.2	4.9	1.47
4b	0.5	0.58	0.49	1.18
4b	2.0	1.20	1.18	1.02

Activation parameters

Activation parameters for the cleavage of **1b** and **4b** were determined by plotting ln k_{obs} against 1/T (the Eyring equation) [27]. The results, deriving from rate measurements at 100°C, 80°C and 60°C, are summarized in Table III.

TABLE III Activation Parameters for Cleavage of **1b** and **4b** in 1.0 $mol \cdot L^{-1}$ D_2SO_4

Temp	k_{obs}, s^{-1}	
K	*1b*	*4b*
373	$6.60 \pm 0.26 \times 10^{-5}$	$1.30 \pm 0.05 \times 10^{-5}$
353	$0.96 \pm 0.04 \times 10^{-5}$	$0.17 \pm 0.01 \times 10^{-5}$
333	$0.13 \pm 0.01 \times 10^{-5}$	$0.016 \pm 0.002 \times 10^{-5}$
	$E_a = 106.6 \pm 5.3$ kJ·mol^{-1}	$E_a = 111.6 \pm 5.6$ kJ·mol^{-1}
	$\Delta H^{\neq} = 103.5 \pm 5.2$ kJ·mol^{-1}	$\Delta H^{\neq} = 108.5 \pm 5.4$ kJ·mol^{-1}
	$\Delta S^{\neq} = 49.1 \pm 2.5$ J·mol^{-1}·K^{-1}	$\Delta S^{\neq} = -50.3 \pm 2.5$ J·mol^{-1}·K^{-1}

Rates of the cleavage in DMSO solution

The phosphonic acid **1b** undergoes cleavage in anhydrous DMSO in the presence of H_2SO_4; it forms the corresponding amine **3b** and some other products, among which polymeric metaphosphoric acids $(HPO_3)n$ were detected by mass spectroscopy. The observed rate was considerably slower than in aqueous solution, but it increased gradually when water was added (Table IV). Surprisingly, the rate reached the maximum for a mixture containing about 50% of water, considerably exceeding the rate of the cleavage in pure water.

TABLE IV Kinetics for the Cleavage of 2-Pyridyl-(N-butylamino)methyl-phosphonic Acid (**1b**) in DMSO Solutions, Containing 1.0 $mol \cdot L^{-1}$ H_2SO_4, at 95°C

Composition of Solvent[DMSO,]			$[H_2O]mol \cdot L^{-1}$	$10^5 \cdot k^a s^{-1}$
$mol \cdot L^{-1}$	*wt. %*			
14.10	100		0	0.40
13.85	98.4		1.0	0.69
12.83	91.8		5.0	2.0
11.60	83.3		10.0	4.5
9.03	66.2		20.0	10.0
3.95	30.0		40.0	7.4
0	0	55.5(100%)		4.6

a. Rates reproducible to ± 5%.

Chemical evidence for metaphosphate formation

Since metaphosphate may be formed in the cleavages, we sought further evidence on this. When the mixture obtained by cleavage of **1b** in pure DMSO was poured into methanol and examined by ESI+Q1MS spectroscopy, we observed **3b** and two other main products, one apparently an adduct of DMSO and diphosphoric acid ($H_4P_2O_7$), and the other the monomethyl ester of trimeric methaphosphate ($MeOPO_2 \cdot 2HOPO_2$). The existence of this ester is evidence of metaphosphate formation.

In turn, the cleavage of diethyl ester [1] of **1b** was carried out in tert-butanol, in the presence of H_2SO_4. After work-up, the reaction mixture was analyzed by G.C.-M.S and ESI+Q1MS spectrometric methods.

Various phosphate esters were found in the reaction mixture, the most abundant being *tert*-butyl phosphate. Finally, when cleavage of **1c** by H_2SO_4 was performed in the presence of anisole, a phosphonylated product, namely 4-methoxyphenylphosphonic acid, was isolated in high yield. This is the most convincing evidence that an electrophilic phosphorus species, such as monomeric metaphosphoric acid or protonated metaphosphoric acid is released during cleavage.

Dissociation constants of pyridyl(amino)methylphosphonic acids

Dissociation constants (pK) of some investigated phosphonic acids (**1b, 1c, 4b** and **4c**) were determined by means of the potentiometric titration. The results are given in Table V. The values of pK_1could not be determined accurately, because of limitation of the method used (potentiometric titration). The next pK values were measured precisely. The pK_2 is presumably referred to protonation of the heterocyclic nitrogen atom (the pK values for 2-substituted pyridines with electron-withdrawing groups are below 2, and for 4-substituted pyridines the corresponding constants are about 4) [48]. The third constant (pK_3) is the second step of dissociation of the phosphonic group. The fourth constant (pK_4) corresponds to the protonation of the amino group in the molecule.

TABLE V Dissociation constants (pK) of phosphonic acids[a] **1b, 1c, 4b, 4c**

Compd.	pK_2	pK_3	pK_4
1b	1.68(6)	5.16(8)	9.99(2)
1c	1.77(7)	5.16(7)	8.94(3)
4b	3.79(2)	5.26(6)	9.18(3)
4c	3.70(6)	5.29(4)	8.04(1)

[a] Standard errors on the last digits are included in parentheses

DISCUSSION

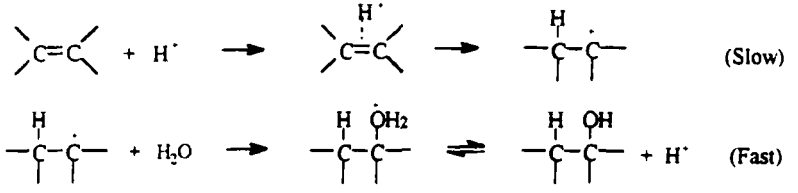
It is clear that protonation of 2-pyridyl of 4-pyridyl(amino)methylphosphonic acids has a fundamental influence on the cleavage of the phosphorus-to-carbon bond in these acids. These acids can be protonated on both

the side-chain amino group and on the pyridine nitrogen atom. These protonations of nitrogen atoms seem to be rapid, pre-equilibrium stages, and therefore should not be involved on the later slow, rate-determining step. The initial protonation of aminophosphonic molecules (structures **2** and **5** in scheme 1) is an indispensable condition for the next step, in which the cleavage of the aminophosphonic acid occurrs.

As seen from our results obtained from kinetic studies, the rates of cleavage are higher in H_2O, than in D_2O (Table II). This observation has a substantial meaning for the proposed mechanism of the cleavage. The $k_H/k_D > 1$ assumes that proton is attendant on a rate-determining step.

Because of the observe isotopic effect, it can be assumed that (besides the rapid initial protonation) the protons are additionally involved in a slow process with a share of pre-protonated phosphonic molecules. The process of protonation may occur also on oxygen of the phosphono group.

In the first approach, the discussed cleavage would resemble a model which has already been proposed for hydration of olefins [17, 24]. This model assumes that formation of a carbocation (from simple olefins and proton) is a rate-determining step. The formed carbocation is then rapidly captured by water. The mechanism for hydration [17] is outlined below (Scheme 2).



SCHEME 2 Mechanism for hydration of olefins

The proton interacting with a double bond of olefin is not free but is supplied by a hydronium ion. One can suppose a transition state, in which the proton interacts electrostatically with both water and olefin. Therefore, the proton transfer from a hydronium ion to olefin will be combined with an existence of the primary isotope effect [24], and also the secondary isotope effect [22, 23]. As a result, the measured net isotope effect is rather small and close to unity [24].

A similar case (a small isotope effect) is observed for hydrogen isotope exchange in aromatic compounds, and as well for desulfonation of aromatic sulfonic acids [17].

All these reactions may be considered as electrophilic substitutions, and they are sometimes designated as A-S_E2 in the literature [17]. Their general equation may be written as follows [17]:

$$\begin{aligned} &S + H_3O^+ \rightarrow SH^+ + H_2O \quad \text{(Rate determining)} \\ &SH^+ \rightarrow \text{Product} + H^+ \qquad \text{(Fast)} \end{aligned} \tag{1}$$

or

$$\begin{aligned} &S + H_3O^+ \rightarrow SH^+ + H_2O \qquad \text{(Rate determining)} \\ &SH^+ + H_2O \rightarrow \text{Product} + H_3O^+ \quad \text{(Fast)} \end{aligned} \tag{2}$$

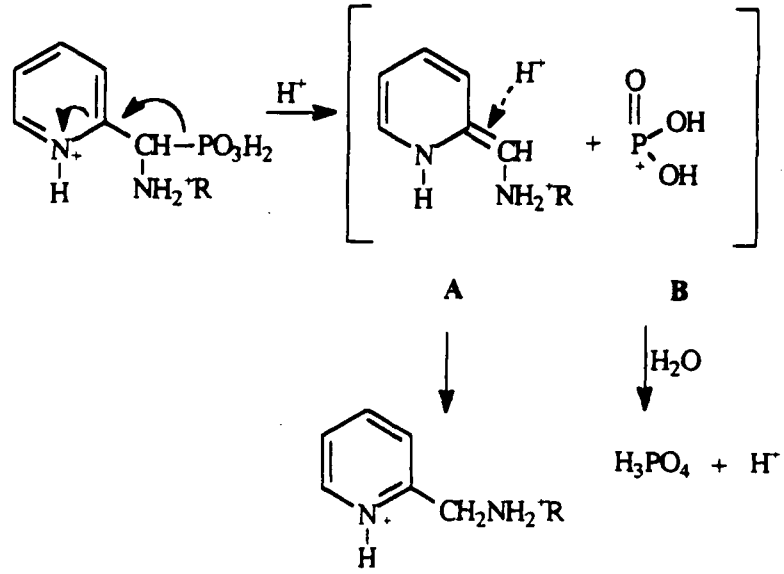
In both equations the rate determining step is the same, bimolecular reaction. The next step of the first equation is an example of unimolecular (A_1) mechanism, because the protonated species (SH^+) decomposes independently to the product, while in the second equation the next step is a bimolecular one (A_2) because water is involved.

The transition state for the cleavage described here would resemble that shown above for the hydration of olefins. When electronic effects in the protonated pyridylphosphonic molecules (structures **2** and **5** in Scheme 1) are considered, a resonance form, resembling an "olefinic" structure would be also considered in this case.

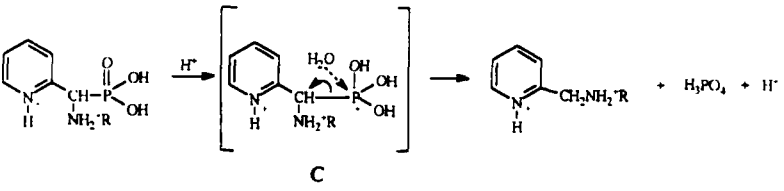
In Scheme 3, we propose a mechanism of the cleavage of 2-pyridyl derivative of aminomethylphosphonic acid as a general example. During reaction, the proton is being bonded on the α-carbon atom in the transition state (**A**), the carbon-phosphorus bond is broken and this in consequence causes a departure of the phosphorus moiety (**B**)

Based on the scheme 3, the proposed mechanism of the cleavage of 2-pyridyl(amino)methylphosphonic acids is not a substitution reaction at phosphorus atom. The mechanism seems to be the electrophilic substitution at α-carbon atom. The proton is an electrophilic agent, and the phosphorus moiety is considered here as a leaving group. The simplest kinetic illustration of the submitted mechanism would be the general equation (1), presented above.

The alternative mechanism, assuming a nucleophilic attack on the phosphorus atom is illustrated below, in scheme 4.



SCHEME 3 Proposed Mechanism for the Cleavage of 2-Pyridyl Derivatives of Aminomethylphosphonic Acid



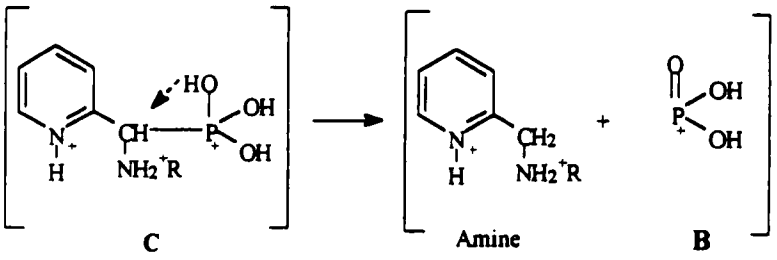
SCHEME 4 The Alternative Mechanism for the Cleavage of 2-Pyridyl Derivatives of Aminomethylphosphonic Acid

The water molecule would attack the protonated phosphorus atom in a transition state (C) to cause an elimination of the heterocyclic moiety and formation of phosphoric acid (H_3PO_4). The eliminated heterocyclic moiety would gain a proton and reorganize to the final heterocyclic amine. The given general kinetic equation (2) would reflect the above mechanism, assuming the attack at phosphorus.

Proposition of the mechanism presuming an nucleophilic attack at phosphorus (scheme 4) seems to be not adequate here, in the view of the authors. There are some arguments to support this assertion. If this cleavage would be a nucleophilic attack of water on the protonated phosphorus atom, one could expect that the parent 3-pyridyl(amino)methylphosphonic acids should undergo a similar cleavage in strong acidic media. Contrary to this, the 3-pyridyl(amino)methylphosphonic acids are stable in strong acidic conditions and do not undergo such a C-P bond cleavage [1]. If a nucleophilic attack on phosphorus would be presumed, there is not a rational reason to explain the stability of the corresponding 3-pyridyl acids in strong acidic solutions. Likewise, there could be expected a similar behaviour (i.e. the cleavage) of the other aminophosphonic acids during a treatment with typical strong mineral acids. On the contrary, most of the aminophosphonic acids and phosphonic acids are stable in acidic conditions [42]. As it is widely known, the aminophosphonic acids are usually synthesized by the acidic hydrolysis (for example by aqueous HCl) of the corresponding aminophosphonic esters, and no such cleavages were reported in most cases. Another argument against the nucleophilic substitution at phosphorus (in this case) is as follow: The C-P cleavage of the **1** or **4** does not occur in aqueous solution of weak acids, such as acetic acid or even oxalic acid. Because of the protonation of the aminophosphonic molecules, even in these weak acids (to some extend), one would also expect an occurrence of such a cleavage, if the nucleophilic attack on the phosphorus atom is assumed.

The observed kinetic isotope effect ($k_H / k_D > 1$) also confirms the proposed mechanism of the cleavage. For the case of a nucleophilic attack on the protonated phosphorus atom, an isotope effect (k_H / k_D) of less than unity should be expected, because concentration of the deuterated phosphorus species in D_2O is higher than concentration of the corresponding protonated species in H_2O (the dissociation constant pK_a in H_2O is higher than in D_2O). It is worthly to add, that the supposed transition state "**C**" (scheme 4) can also split unimolecularly to the heterocyclic amine and protonated metaphosphate (**B**) without interference of a nucleophile. Such situation is shown in scheme 5.

In the view of the authors, the described cleavage is a particular example of transformation caused by the presence of the specific heterocyclic systems in the aminophosphonic molecule (i.e. 2- and 4-pyridyl moieties). The driving force for such a cleavage would be an apparent transfer of a



SCHEME 5 Unimolecular Splitting of the Protonated 2-Pyridyl(*N*-alkylamino)methylphosphonic Acid Molecule

positive charge from the heterocyclic nitrogen to a phosphorus atom, which results from the electronic effects in the considered heterocyclic phosphonic acid molecules. The "positive" phosphonic group would be able to release a protonated metaphosphate. It is obvious, that it happens only for 2- and 4-pyridyl derivatives. Other heterocyclic systems, substituted at 2- or 4-positions should demonstrate a similar behaviour. For example, we found lately that the oxygen heterocyclic derivative of aminophosphonic acid, namely; chromone-2-yl(N-benzylamino)methylphosphonic acid was cleaved in aqueous HCl to form the corresponding amine and phosphoric acid [43]. The parent chromone-3-yl phosphonic derivatives were stable in strong acidic conditions, as it was expected [43].

Electrophilic substitution in which the proton replaces another group is rather rare. An example of a similar reaction is a desulfonation of aromatic sulfonic acids in diluted mineral acids[17,34], or the cleavage of methylmercuric iodide [33] or other organometalics by strong mineral acids [34]. Decarboxylation of the carboxylic acids in mineral acids is also considered as an example of such an electrophilic substitution [34]. A replacement of a sulfonic group by NO_2^+ (the *ipso* substitution) in aromatic systems may be also a similar example [34].

Such a kind of the electrophilic substitution was also postulated for a cleavage of *o*- and *p*-substituted aromatic phosphonic acids. Some *o*- and *p*-methoxy aromatic phosphonic acids were cleaved in aqueous H_2SO_4, HCl or HBr to form the corresponding substituted arene and phosphoric acid [42, 44a,b]. Cleavage of the C-P bond in *p*-methoxyphenylphosphonic acid by aq. H_2SO_4 was investigated kinetically by Viout and Rumpf[44b]. They found that the reaction was first order in phosphonic acid, but more

complex in H^+. Thus, in lower concentration of H_2SO_4(< 30%) the reaction rate increased with the square of the H_2SO_4 concentration, but above 30% H_2SO_4 the rate gradually decreased and become markedly slowed, as the concentration approached 60%. They also proposed a mechanism assuming an electrophilic replacement of phosphonic group by H^+, and postulated a positively charged metaphosphate ($PO_3H_2^+$), as a leaving group. These data are in a striking agreement with our findings.

In our case, the leaving phosphorus group may be a reactive metaphosphate molecule or the protonated species **B**, (scheme 3) which is able to react with water to form phosphoric acid. The evidence that the leaving group may be a metaphosphate was checked by a separate experiment, in which a cleavage of the phosphonic acid **1c** was carried out in the presence of anisole as a trapping agent. The product (the 4-methoxyphenylphosphonic acid), resulting from an electrophilic attack of the assumed metaphosphate (or the corresponding protonated species) on the aromatic ring of anisole was isolated in a considerable yield (~50%).

The cleavage of diethyl ester[1] of **1b** was also performed in *tert*-butanol. If the metaphosphate was formed, it could react with *tert*-butanol to form tert-butyl phosphate [39]. Phosphate esters of tertiary alcohols are not readily prepared by conventional means, and the simplest explanation for the formation of such esters is an electrophilic attack of the metaphosphate on the alcohol [12]. Formation of a mixture of various ethyl and *tert*-butyl phosphate esters in this case might be an additional proof for the metaphosphate formation. Another evidence for a metaphosphate is appearance of polyphosphoric acids $(HPO_3)_n$ during cleavage in a pure DMSO solution. The polyphosphoric acids are expected to be formed from a metaphosphate moiety, in the absence of water.

Entropy of Activation

The use of $\Delta S^{\neq}$ for distinguishing between uni- and bimolecular mechanisms is based upon the greater ordering necessary in the transition state of a bimolecular reaction. The entropy of activation observed for a cleavage of **1b** or **4b** may be also helpful in our case. For the unimolecular reaction the $\Delta S^{\neq} \sim 0$ e.u., and for bimolecular one the $\Delta S^{\neq} \sim -20$ e.u. (~ -83.6 $J \cdot mol^{-1} \cdot K^{-1}$) are expected (the data given are for substrates for which the point of protonation is a weakly basic oxygen atom)[29]. The observed $\Delta S^{\neq}$ for the cleavage reaction actually consists of $\Delta S^{\neq}$(protonation)

$+ \Delta S^{\neq}$(cleavage). Entropies of protonation of weak bases appear to vary with the acidity of the conjugated acid, becoming negative for very acidic ones[30]. $\Delta S^{\neq}$ for protonation of weak oxygen or nitrogen bases is approximately −20 e.u.(-83.6 $J \cdot mol^{-1}K^{-1}$), or more negative [5, 33]. At this point, it is hard to predict what is the participation of $\Delta S^{\neq}$(protonation) in the whole $\Delta S^{\neq}$ for the cleavage reaction. One can suppose that the $\Delta S^{\neq}$(protonation) in this case should be also negative. Therefore, the measured small values of $\Delta S^{\neq}$for the **1b** and **4b** [~ −50 $J \cdot mol^{-1} \cdot K^{-1}$ (~ −12 e.u.), Table III] could support a unimolecular mechanism of the cleavage.

Dependence of Rate on Acidity

Pyridyl(amino)methylphosphonic acids **1, 4** undergo cleavage with *log k* linearly dependent on H_o, for lower concentrations of sulfuric acid (Figure 1). However, for higher concentrations of acid the dependence is not linear, and plots show a curvature in direction of decreasing absolute slope with increasing H_o. The slopes for linear dependences are 1.09 for **1b** and 0.86 for **4b**. According to Zucker-Hammett hypothesis such a dependence indicates an A_1mechanism [17], and it would be at least the case for a cleavage in lower concentrations of sulfuric acid. The Zucker-Hammett hypothesis has been widely criticized [18, 31]and some new solutions have been delivered. According to the Bunnett method [18–21], the A_1 and A_2 mechanisms can be distinguished by plotting the log $k_{obs} + H_o$on logarithm of water activity in solutions of the used mineral acids. The slopes (*w* values) can be helpful in the distinguishing between these mechanisms.

The plots (Figure 2) exhibit a good linearity for higher concentrations of sulfuric acid. The slopes (for **1b**: $w = 14.4$, for **4b**: $w = 19.1$) are exceptionably high. Mechanistic interpretation of the obtained *w* values, according to the Bunnett classification [19], indicates that water acts as a proton transfer agent in the rate-determining step. This result would also not exclude an occurrence of a nucleophilic attack of water at phosphorus in the concentrated solutions of sulfuric acid.

Despite that Zucker-Hammett and Bunnett methods are rather old-fashioned theories, frequently criticized [31,32], but in the view of the authors, these methods have significance in an explanation of some of the acid-catalyzed reactions, which may be applied for the cleavage of 2- and 4-pyridyl(amino)methylphosphonic acids.

Kinetics in DMSO solution

Rate of the cleavage of **1b** in pure DMSO is about ten times smaller than that found in water. It could be explained by the fact, that sulfuric acid is less dissociated in DMSO, and the activity of protons is lower than in water. Addition of water to DMSO solutions considerably increases the rates of cleavage. Surprisingly, for a mixture containing more than 10 moles of water (≅ 83% DMSO by weight) the rates are becoming faster than in pure water, and achieve a maximum value for a solution containing approximately half-and-half DMSO and water (Table 4). Further addition of water decreases the rate of cleavage. The highest rate, in a mixture 1:1 of DMSO and water may be caused by greater activity of the protons, since in this solution protons are less solvated. These kinetic results indicate (Table IV) that the water molecule is rather not involved (as a nucleophile) in this cleavage.

Substituents at amino group

The rates are the highest for benzyl derivatives (**1c, 4c**) of phosphonic acids, and they are approximately two times greater than for both butyl derivatives (**1b, 4b**). The rates decreased in the following order of substituents: $CH_2Ph > Bu > NH_2 > Ph$. Influence of the chemical character of the substituent on rates is not clear. The basicity of individual substituents as a criterion is not the case. In this sequence, the butylamino group is the most basic. Likewise, the 2-pyridyl derivatives (**1a-d**) are cleaved about 5 times faster, than the corresponding 4-pyridyl derivatives (**4a-d**), in spite of that the basicity of the 4-substituted pyridines are considerably greater than 2-substituted ones.

According to the values of dissociation constants obtained for some 2-pyridyl (**1b, 1c**) and 4-pyridyl-phosphonic acids (**4b, 4c**) (Table V), it appears to be certain that the acidity of individual compounds has a distinct influence on the rate of the cleavage. The pK_{a2} (assumed to be a protonation of the heterocyclic nitrogen) for 2-pyridyl-phosphonic acids is about two units smaller than for the corresponding 4-pyridyl derivatives (Table V). The corresponding rates for 2-pyridyl derivatives are 5–6 times higher. Likewise, the pK_{a4} values (protonation of the amino group) are larger by about unity for *N*-butyl derivatives than for the corresponding *N*-benzyl derivatives, and the *N*-benzyl derivatives are cleaved about two

times faster than *N*-butyl derivatives. In turn, the obtained results of pK_{a3} (Table V) suggest that the range of the second ionization of the phosphonic group has no effect on the rate of the cleavage.

The observed dependence of dissociation constants of the pyridyl(amino)methylphosphonic acids on rates of the cleavage, requires more detailed studies.

EXPERIMENTAL SECTION

2-Pyridyl (**1a-d**) and 4-pyridyl(amino)methylphosphonic acids (**4a-d**) and the corresponding diethyl esters were prepared according to the procedures [1,2].

^{31}P NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz spectrometer (121.51 MHz), in D_2O solutions. In the case of ^{31}P NMR spectra in H_2O, or in non-deuterated DMSO solutions, a lock system in the spectrometer was pre-locked for D_2O, or DMSO-d_6, respectively. Phosphorus signals were negative if upfield of 85% H_3PO_4.

G.C.-M.S. analyses were recorded on a Helwett Packard HP 5971A apparatus, at an ionization potential of 70 eV, equipped with HP-1 (25 m) capillary column. ESI+Q1MS analyses were done on a Finnigan TSQ 700 instrument (electrospray ionization, on mode: ESI+Q1MS).

Procedure for Kinetic Runs

The stock solutions of pyridyl-phosphonic acid (**1** or **4**) in aqueous solutions of mineral acid (H_2SO_4, HCl, HBr) were prepared. The solutions were composed with appropriate phosphonic acid ($c = 0.2$ mol·L^{-1}) and with strong mineral acid ($c = 0.5, 1.0, 1.5, 2.0$ mol·L^{-1}, respectively). Similar solutions were made in D_2O, using appropriate pyridyl-phosphonic acid and deuterated mineral acid. The samples (a 0.5 mL aliquot of a solution) in NMR tubes were thermostated at 95°C for a desired period of time (2, 4, 6, 8h, respectively), cooled, and the NMR spectra were recorded. The kinetic runs in DMSO solutions, or for determining activation parameters were done similarly. Kinetic runs were repeated three times. In all cases a pseudo-first-order dependence was obeyed very well (with one exeption, see Table I). The obtained k_{obs} were means of each three kinetic runs and were reproducible within ± 5%.

The Cleavage of 1b in DMSO. Analysis of the Products

A solution of **1b** (24.4 mg, 0.1 mmol) in dry DMSO (0.5 mL), containing H_2SO_4 (49 mg, 0.5 mmol) was heated at 95°C for 70 h protected against moisture, and the ^{31}P NMR spectrum of the mixture was recorded: 11.10(s. assigned as the formed phosphoramidate [12, 35]: **3b**·HPO_3, 28.1%). 7.41(s, unreacted **1b**, 22.9%). –0.93[(s, assigned as an adduct: DMSO·$(HPO_3)_n$, 49% (the sum of integration of all phosphorus peaks = 100%)].

Then, the reaction mixture was poured into methanol (1.0 mL) and left for 24 h. The obtained solution was analysed by the ESI+Q1MS spectrometric method. In the spectrum of a mixture, the following mass peaks were found: 257.1 (assigned as an adduct: DMSO·$H_4P_2O_7$, percentage of abundance: 100%), 255.1(assigned as the ester: CH_3OPO_2·$2HPO_3$, 24%), 245.1 (assigned as the phosphoramidate: **3b**·HPO_3, or unreacted **1b**, 8.5%), 177.1(an adduct: DMSO·H_2SO_4, 28%), 165.1(amine **3b**, 32%), 119.1(unknown product, 30%), 79.0 (DMSO, 34%).

The Cleavage of 1c in the Presence of Anisole. Isolation of 4-Methoxyphenylphosphonic Acid

2-Pyridyl(N-benzylamino)methylphosphonic acid (0.50g, 1.7 mmol), anisole (1.9 g, 17 mmol), and sulfuric acid (1.7 g, 17 mmol) in nitromethane (30 mL) were refluxed for 12 hr. and cooled. The separated crystals were filtered off, washed with 5 ml nitromethane and dried. A white product was obtained, which resulted in 4-methoxyphenylphosphonic acid, according to the literature data [44, 46, 47]. Yield : 0.21 g (63%). M.p. 157–158°C. Lit.[46] m.p. 158°C. ^1H NMR (D_2O): 7.62(d, 2H, J=8.7 Hz), 6.92(d, 2H, J= 8.6 Hz), 3.72(s, 3H, OCH_3). ^{31}P NMR (D_2O): 6.965(s).

The Cleavage of Diethyl Ester of 1b in tert-Butanol. Analysis of the Products

Diethyl 2-pyridyl(N-butylamino)methylphosphonate [1] (0.36g, 1.2 mmol) was dissolved in *tert*-butanol (5 mL), containing 0.35g (3.6 mmol) H_2SO_4. The solution was heated at 75°C for 24 h, protected against moisture. The solvent was evaporated, the residue neutralized to pH ≡ 7 with aqueous 1mol·L^{-1} K_2CO_3 (3.6 mL), and extracted with methylene chloride

(50 mL). The extract was dried (anh. Na_2SO_4). filtered and evaporated to give a small amount of thick oil (~50 mg), which was analysed by G.C.-M.S. According to G.C. data, the oil proved to be a mixture of mainly ethyl *tert*-butyl phosphate and the amine **3b**. There were also small amounts of other esters: diethyl *tert*-butyl phosphate [38] and mono-*tert*-butyl phosphate.

Data for amine **3b** [1]: Retention time: 10.90 min. Mass (abundance, %): 162(M-2, 1%), 133(6.2%), 119(100%), 106(M+1-Bu, 6.4%), 92(2PyCH$_2$, 53%), 78(9.5%), 65(14.5%), 27(11%).

G.C.-M.S. data for diethyl *tert*-butyl phosphate: Retention time: 8.43 min. Mass (abundance, %): 210(M, 3.1%), 196(2.5%), 154(M-*t*Bu+1, 2.4%), 139(2.4%), 121(4.5%), 111(7.0%), 97(16%), 83(38%), 69(22%), 57(*t*-Bu, 100%), 43(31%).

G.C.-M.S. data for ethyl *tert*-butyl phosphate: Retention time: 11.17 min. Mass (abundance, %): 181(M-1, 0.2%), 153(M-Et, 25%), 119(5%), 97(65%), 83(12%), 69(7%), 57(*t*-Bu, 100%). G.C.-M.S. data for *tert*-butyl phosphate: Retention time: 20.80 min. Mass (abundance, %): 153(M-1, 9.5%), 123(0.5%), 113(10.5%), 97(29%), 83(8.5%), 69(4.5%), 57(*t*-Bu, 100%). ^{31}P NMR($CDCl_3$) of the oil: 0.71[s, integration (relative intensity): 92%, ethyl *tert*-butyl phosphate, Ref. 39: $\delta_P = -2.9$], 7.64(s, 8%, diethyl *tert*-butyl phosphate, Ref. 38: $\delta_P = 4.0$).

The obtained G.C.-M.S. data for ethyl *tert*-butyl phosphate and diethyl *tert*-butyl phosphate [36- 38] were in agreement with the data of authentic samples, which were synthesized independently, according to the methods published earlier [36,37].

Potentiometric Measurements

Potentiometic titrations of pyridyl(amino)methylphosphonic acids (**1b, 1c, 4b, 4c**) were performed at 25°C with a MOLSPIN automatic titration system, using NaOH as a titrant in the presence of 0.1 mol·L^{-1} KNO_3. Changes of pH were monitored with a combined Rassell electrode [40]. The samples (a 2.0 mL aliquot of solution, c = 2· 10^{-3} mol·L^{-1} of appropriate phosphonic acid) were threefold titrated. The obtained potentiometric data were analyzed using SUPERQUAD program [41]. Standard deviations of pK_a values were referred to the statistical errors only.

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