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Associative *vs*. dissociative mechanism of P-C bond breaking in α-aminophosphonates leading to phosphoric acid [P(V)] derivatives

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Dedicated to Prof. Jacek Młochowski on the occasion of his 80th birthday

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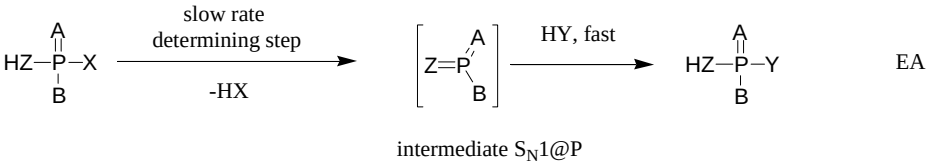
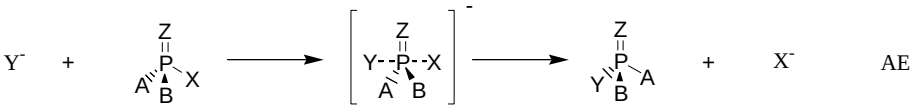
Abstract

The α-aminophosphonates are relatively easily protonated on phosphoryl oxygen in acidic conditions due the neighboring amine group effect. Protonation of phosphoryl oxygen makes the phosphorus atom highly electrophilic and suitable for decomposition with P-C bond breaking to P^{III} or P^{V} decomposition products. The process of decomposition to P^{III} products has a large positive entropy value (198.8 [J/K.mol]) which indicates an elimination mechanism. High negative entropy of activation -72 [J/K.mol] for decomposition to P^{V} derivatives - suggests that it undergoes a nucleophilic substitution mechanism via a trigonal-bipyramidal intermediate or transition state. Many other arguments for such a statement are discussed.



a) intermediate $S_N1@P$

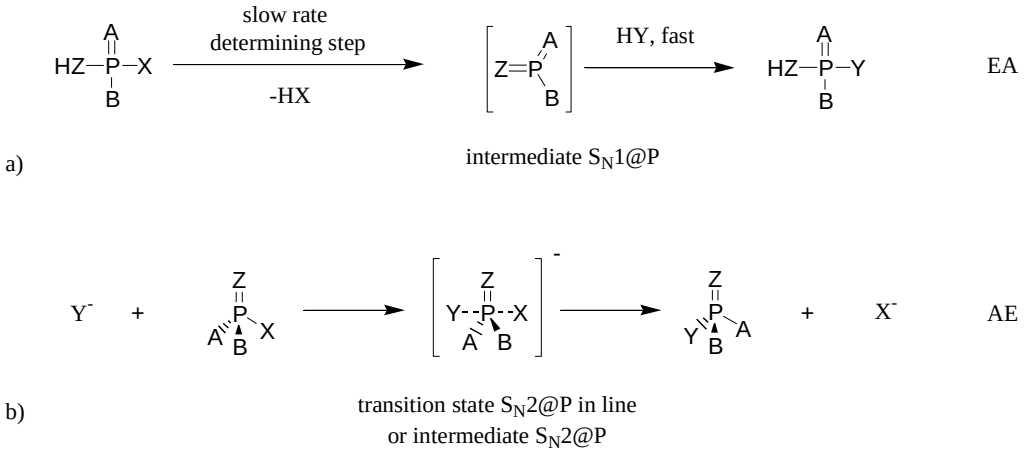


b) transition state $S_N2@P$ in line or intermediate $S_N2@P$

Keywords: Aminophosphonate, PC bond breaking, kinetic studies, associative vs. dissociative, entropy

Introduction

Phosphoryl transfer is an essential part of many biological processes as well as in chemistry as a whole.[1-3] Many efforts have been made to uncover the pathways by which the P=O centre can react with nucleophiles. In general, two mechanisms have been proposed: $S_N1@P$, in which pentavalent three-coordinated species would be intermediates (Scheme 1a)[4,5] (in some papers it is described as EA – elimination-addition) and $S_N2@P$, which proceeds via a pentavalent pentacoordinated transition state or intermediate (Scheme 1b) [4,6] (in some papers denoted by AE – addition-elimination).



Scheme 1. (a) $S_N1@P$ -associative elimination-addition mechanisms (EA); (b) $S_N2@P$ -addition- elimination mechanisms (AE).

The metaphosphate monoanion as a possible reaction intermediate has been discussed since 1955.[7] It was however concluded later that the phosphoryl transfer process is rather disinclined towards reaction by the dissociative $S_N1@P$ mechanism – very rarely when Z was a carbon[3] atom. The dissociative mode of P-C (phosphorus-carbon) bond breaking could also be preferred in the case of very sterically hindered phosphorus compounds and especially in non-nucleophilic or very weakly nucleophilic solvents. Calculations have shown that a pentavalent tricoordinated structure cannot be an intermediate in aqueous media since water is too strong a nucleophile.[7] Such reactions were observed by Breuer and Mahajna in highly polar weakly nucleophilic non-aqueous media.[8,9]

Water substitution generally proceeds rather by an associative mechanism $S_N2@P$ with formation of a pentacoordinated pentavalent phosphorus structure. It resembles that occurring in bimolecular nucleophilic substitution reactions at saturated carbon atom and is called $S_N2@P$ in line. If the transition state is long-lived enough to turn into an intermediate, then the mechanism is referred as $S_N2@P$,[10] (Scheme 1b). The intermediate can undergo pseudorotation[11] prior to departure of the leaving group and in such cases retention or inversion of configuration at phosphorus will be observed depending on the number of pseudorotamers.

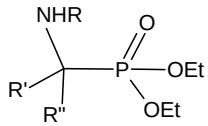
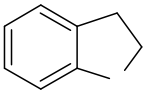
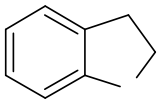
There has long been discussion in the literature on whether phosphorus amides or chlorides undergo hydrolysis via dissociative or associative mechanism.[5,12] Finally Harger and others[13] verified the results and stated, after additional experiments, that acid-catalyzed diphenylphosphinic amide hydrolysis is retarded by substituents which sterically hinder attack at phosphorus. This led him to the conclusion that such sensitivity to steric hindrance is consistent with an associative (AE) mechanism. Similar conclusions, based on numerous

stereochemical studies[14,15] have been formulated for other phosphoryl derivatives. In the majority of cases[16-18] nucleophilic substitution at phosphorus affords inversion of configuration, which is an indication of the formation of a pentacoordinated pentavalent trigonal- bipyramidal transition state or intermediate.

Due to the strength of the phosphorus-carbon bond (P-C) α-aminophosphonates/α-aminophosphonic acids are stable compounds. Some of them however undergo P-C cleavage leading to phosphoric acid P^{III} by means of ninhydrin[19] H_2O_2[20], $NaIO_4$[21] aqueous bromine[22] and aqueous halogens[23]. There are also some α-amino-phosphonates/α-aminophosphonic acids that are labile in acidic or basic solutions and which decompose with breaking of the P-C bond. Such reaction can proceed by either of the mechanisms described above, i.e. associative or dissociative. Gancarz[24] has found that 1-*(N*-phenylamino)-1-phenyl methyl-phosphonic esters decompose with breaking of the P-C bond relatively easily in acidic aqueous solutions at elevated temperatures to P^{III} (derivatives of phosphonic acid H_3PO_3). Boduszek[25,26] observed that some pyridyl aminomethylphosphonates decompose to P^V derivatives and proposed alternative mechanisms for the decomposition of pyridyl aminomethylphosphonic acids to P^V derivatives. He performed some experiments in non-aqueous media and found that they follow S_N1@P mechanism via formation of tri-coordinated P^V intermediates. Experiments in non-aqueous media cannot however be a proof for the reaction mechanism in aqueous solutions. Gancarz[6] was the first to propose that elimination of α-aminophosphonates in acidic aqueous solution to P^{III} derivatives is an S_N1@P process, whereas the decomposition to P^V in aqueous solutions occurs via the attack of water on the phosphorus atom - S_N2@P.

Examples of labile α-aminophosphonates are listed in Table 1.[6,27]

Table 1. Diethyl α-aminomethylphosphonate decomposition products

	**R', R"**	**R**	Decomposition products[a]			Refs.
			1h	6h	24h	
1	Ph, H	CH_2Ph	100:0:0	100:0:0	100:0:0	36,57,40
2	Ph, H	Ph	32:68:0	0:100:0	0:100:0	36,40
3	Ph, H	2Py	100:0:0	100:0:0	100:0:0	36,40
4	2-Py, H	Ph	78:0:22	25:0:75	0:0:100	36,40
5	3-Py, H	Ph	100:0:0	100:0:0	100:0:0	40
6	4-Py, H	Bu	92:0:8	83:0:17	62:0:38	40
7		$(Ph)_2CH$	28:72:0	28:72:0	28:72:0	36,47,40
8		H	100:0:0	100:0:0	100:0:0	36,47,40

[a] The molar ratio of undecomposed product, phosphorous acid, phosphoric acid derivatives respectively, determined by ^{31}P NMR measurement after 1, 6, 24 hours reaction in 20% DCl at 91 ^oC.

In the present work we have performed studies in water solution including the kinetic measurement of ester decomposition which allowed us to study the role of nucleophile, steric influence of substituents at

phosphorus and the role of leaving group on the reaction rates. We have compared also the P-C bond breaking processes leading to P^{III} and P^{V} decomposition products.[24,27,28]

Results and Discussion

The structure of aminophosphonate in acidic media, protonation equilibria

We have observed, that with increasing acid concentration the chemical shift for the phosphorus at $^{31}P\{^{1}H\}$ NMR of the phosphonic acid moves up field from ca 5.4 to 4.8 ppm. At the same time the width of the signal is substantially increased. Both the chemical shift and line broadening are correlated, as shown in Figure 1.

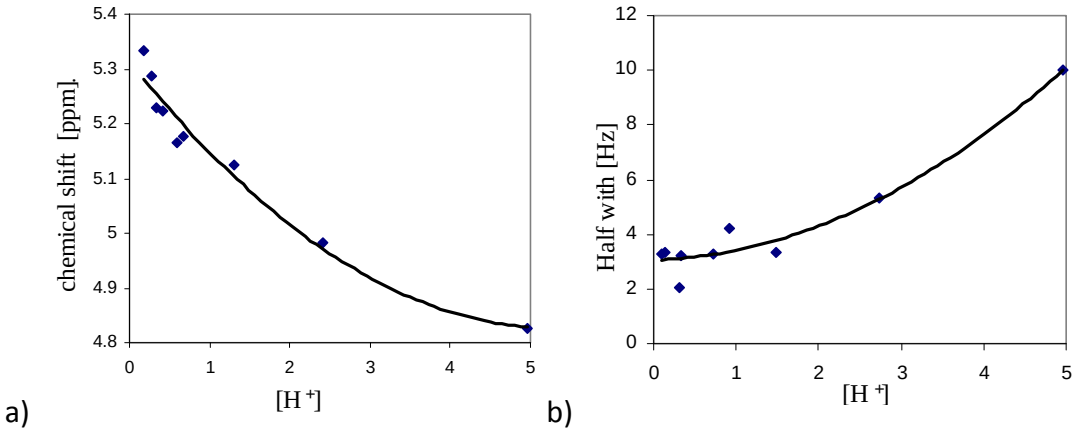
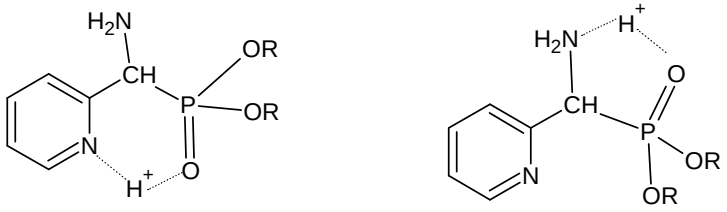


Figure 1. (a) Chemical shift of the ^{31}P NMR signal [ppm] as a function of acid concentration [mol/dm^3 HCl], (b) Half width of the ^{31}P NMR signal [Hz] as a function of acid concentration [mol/dm^3 HCl].

Haake and Ossip[10] found that phosphinic acids, phosphine oxides and phosphinate esters behave in strong acid as Brönsted bases. Protonation of dialkyl phosphites was observed by Hudson and Roberts.[29] Variation in the chemical shift and coupling constant as a function of pH of solutions of compounds containing a phosphoryl group has been known since the 1970s. This phenomenon, in the case of dimethyl hydrogen phosphite in carboxylic acids, has been interpreted in terms of varying degrees of association of the acidic proton with the phosphoryl oxygen.[30,31,32] The equilibrium constant in that case (pK) was estimated as ca. –5.[33] Such interactions are observed in the crystalline state in many compounds containing phosphoryl group. For example 1-*(N*-phenylamino)-1-phenyl-methylphosphonic acid was analysed by Ruźić-Toruś.[34]

In the case of α-aminophosphonates there are two centers of basicity, the amine nitrogen and the phosphoryl oxygen.[35] We have performed calculations of the possible equilibria that could exist in α–amino-phosphonates[36,37] and we have found that the presence of a basic amine group in close proximity to the phosphoryl oxygen helps in protonation of the latter by the neighboring group effect. In this case the calculated energy barrier for the shift of a proton from the vicinity of nitrogen toward the vicinity of the phosphoryl oxygen via the hydrogen bond interaction was found to be about 9 kcal/mol. In pyridyl derivatives, additionally a proton on a pyridyl nitrogen atom takes part in this type of interaction (Scheme 2).



Scheme 2. The structure of hydrogen bonding in the 2-pyridyl-aminomethylphosphonic esters.[36,37]

The observed changes of chemical shift and half width of the ^{31}P NMR signal have been supported by calculation,[37] and they strongly indicate the existence of an equilibrium between species protonated on nitrogen and phosphoryl oxygen in aminophosphonates. The hydroxyphosphonates do not behave in this way, which additionally suggests the significant influence of the neighboring amino group.

Kinetic studies; the role of the nucleophile on the PC bond breaking

Dependence of rate of decomposition on the acidity of the reaction medium. The observed rate of decomposition with P-C bond breaking toward to P^V derivatives is almost linear at low concentrations of acid, then reaches a maximum and drops down at high concentration of acid (Figure 2).

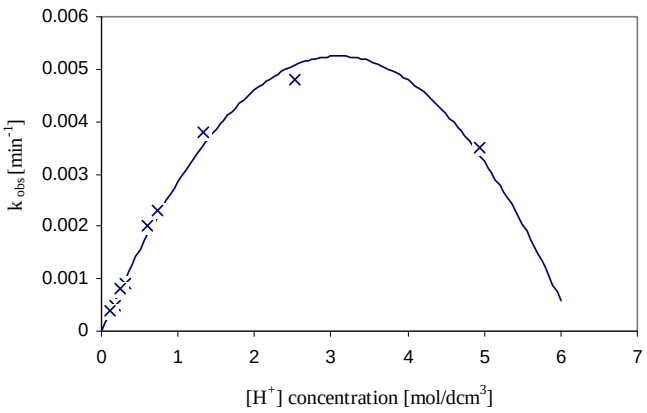


Figure 2. The rate of the decomposition of diethyl esters of 1-(*N*-butylamino)-1-(2-pyridyl) aminomethyl-phosphonic acid as a function of acid concentration. Points are the experimental data, solid line corresponds to the calculated second order best fit curve (details are explained in the text).

Similar changes of the reaction rate at high concentrations of acid were observed independently by Boduszek[26], Kiersnowska[27] and Doskocz[37]. An attempt at improvement of the linearity of the curve by applying the Zucker-Hammett acidity function was without success.[26] We have found that the observed changes can be well approximated by the second order polynomial. This is shown in Figure 2, where the solid line corresponds to the best second order approximation of the data points.

This phenomenon and the character of the changes can be explained by considering water as a nucleophile in an S_N2@P reaction. In high concentrations of an acid the concentration of nucleophile i.e. free water molecules, is reduced since most of water molecules are in the hydration sphere of ions in the solution and are no longer nucleophilic.

For the $S_N2@P$ reaction, we can write:

$$SH^+ \rightleftharpoons S + H^+$$
$$SH^+ + H_2O \rightarrow P1 + P2$$

Where S means substrate and one can formulate the kinetic equations for the reaction rate:

$$K = \frac{[H^+][S]}{[SH^+]} \qquad \Rightarrow \qquad [SH^+] = \frac{[H^+][S]}{K}$$

$$r = \frac{dc}{dt} = k[SH^+][H_2O]$$

$$\frac{dc}{dt} = k[H_2O]\frac{[H^+][S]}{K} = k_{obs}[S]$$

$$k_{obs} = \frac{k}{K}[H_2O][H^+]$$

Assuming that ions from each molecule of added hydrogen chloride are hydrated by n molecules of water we can calculate the number of free (nucleophilic) molecules of water as $C_{o\,H_2O} - nC_{H^+}$. This leads to a second order polynomial:

$$\text{Where: } k_{obs} = \frac{k}{K} \cdot \left([H_2O] - n \cdot [H^+]\right)[H^+] = \frac{k}{K} \cdot \left([H_2O] \cdot [H^+] - n \cdot [H^+]^2\right)$$

For the $S_N1@P$ reaction we can write:

$$[SH^+] = \frac{[H^+][S]}{K}$$

$$r = \frac{dc}{dt} = k[SH^+] = k\frac{[H^+][S]}{K} = k_{obs}[S]$$

$$\text{Where : } k_{obs} = \frac{k}{K} \cdot [H^+]$$

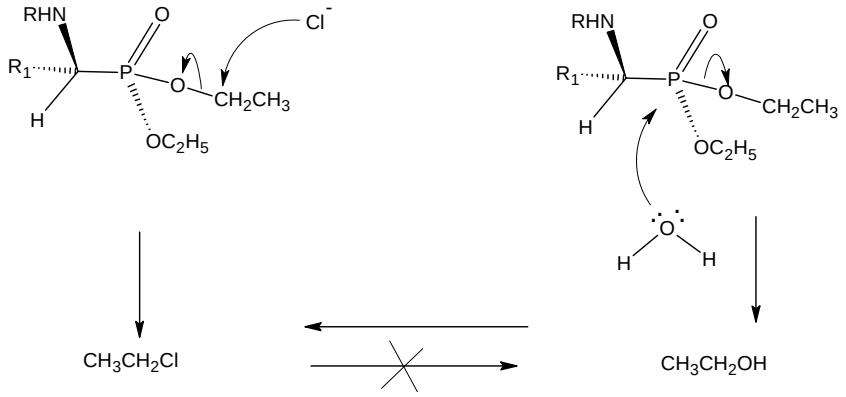
From the above equations one can see that the dependence of the observed reaction rate, k_{obs}, on the concentration of $[H^+]$ should be linear for the $S_N1@P$ reaction or parabolic in nature for the $S_N2@P$. The observed parabolic character of the changes (Figure 2), indicates then, a bimolecular nature of the studied decomposition.

Not knowing the equilibrium constant, we are not able to calculate the reaction rate k, but we can calculate the ratio k/K. In both reaction mechanisms this ratio should be constant. Assuming the $S_N2@P$ mechanism, the calculated k/K in the performed experiment varies from $6.64 \cdot 10^{-5}$ to $5.15 \cdot 10^{-5}$ with the average value of $6.12 \cdot 10^{-5}$ and standard error of estimation equal $4.94 \cdot 10^{-6}$. A similar calculation for the $S_N1@P$ mechanism leads to k/K value varied from 1411.4 to 466.1 with average value 361.6 and standard error of estimation equal 311.5. The obtained data then fit only with the $S_N2@P$ mechanism.

The equation for k/K for $S_N2@P$ can be also used to estimate the number n of molecules involved in solvolysis of hydrogen and chloride ions. The best fit (with the smallest error) was obtained for *n*=9. This is

very close to the sum of typical coordination numbers for hydrogen H^+ (typical is 4) and Cl^- (typical is 6)[38] and this additionally supports the bimolecular mechanism with water as a nucleophile.

Rate of hydrolysis of diesters *vs*. dealkylation. When the dialkyl ester of 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic is heated at 87 ^oC. and the process is carefully monitored at the very early stage of decomposition, one can observe the formation of the monoester of 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic acid along with the formation of chloroethane (at 3.35 ppm as a quartet) and ethanol (at 3.45 ppm as a quartet) (Scheme 3 and Figure 3).



Scheme 3. Dealkylation vs. hydrolysis of α-aminophosphonates.

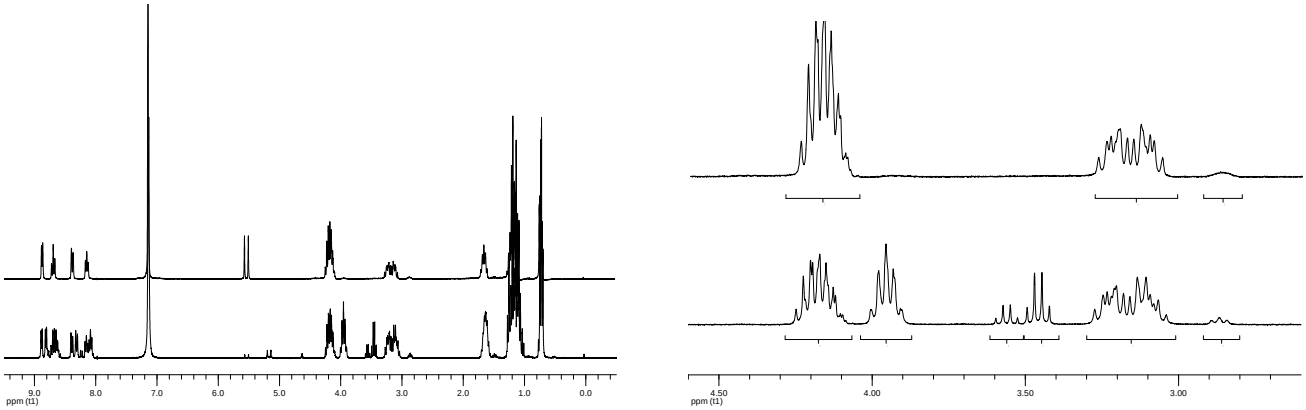


Figure 3. Hydrolysis vs. dealkylation of diethyl esters of 1-(*N*-butylamino)-1-(2-pyridyl) aminomethyl-phosphonic acid (full spectrum left and expanded right). For details see text.

The processes were clearly observed by ^1H NMR spectroscopy, see Figure 3. Chloroethane and ethanol were identified as such by the independent addition of ethanol and chloroethane to the NMR tube. At this temperature and certain stage of the reaction the decomposition with P-C bond breaking was not observed as monitored by $^{31}P\{^1H\}$NMR.

Chloroethane is formed by an dealkylation process well known in the chemistry of phosphorus esters. Formation of ethyl alcohol may come from hydrolysis of chloroethane or hydrolysis of an aminophosphonate ester in an S_N2@P type nucleophilic substitution reaction at phosphorus. The conversion of chloroethane to ethyl alcohol in the reaction conditions studied must be ruled out, for it is contradicted by the principle of

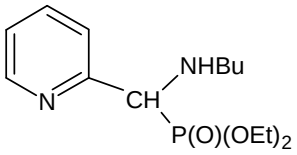
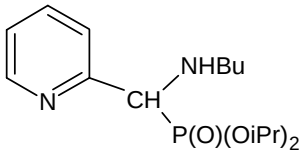
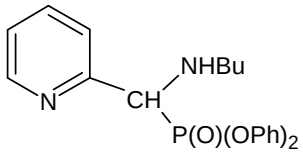
organic chemistry and also the result of our own independent experiment. The conversion of chloroethane to alcohol is described in the literature as proceeding at elevated temperatures and in the presence of catalysts. The same is true for the conversion of alcohol to alkyl chloride, except for tertiary alcohols, see for example.[39]

In our experiment conducted in a 20% solution of hydrogen chloride, the concentration of free water molecules (not protonated and not involved in hydratation, is very low) so this additionally diminishes the possibility of hydrolysis of chloroethane. The stability of chloroethane and ethyl alcohol in the studied conditions is proven by two facts: first, the relative concentration of the products (ethyl alcohol and chloroethane) does not change with time and second : the existence of an equilibrium between alcohol and alkyl chloride is not observed when the alcohol is kept for the duration of experiment in a 20% solution of hydrogen chloride.

This experiment reveals that the phosphorus atom in aminophosphonates is suitable for nucleophilic substitution $S_N2@P$ via a pentacoordinate intermediate or transition state if a relatively good leaving group is present.

Steric effects on the rate of decomposition. Studying the kinetics of decomposition for diethyl, diisopropyl and diphenyl esters of pyridyl aminomethylphosphonic acid derivatives by $^{31}P\{^1H\}$NMR, at the very early stage we were able to measure the influence of the size of substituent on phosphorus on the reaction rate of decomposition of the diester (Table 2). Analysis of the data from Table 2 indicates that the larger the substituent at phosphorus the slower is the decomposition reaction.

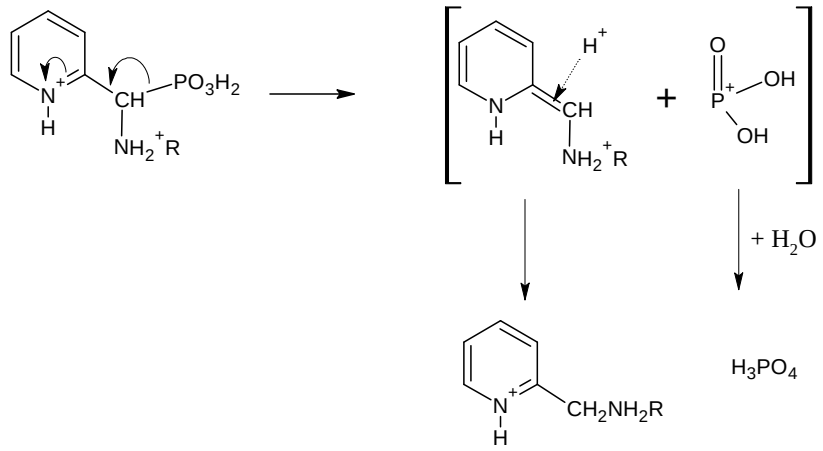
Table 2. Rate constants of decomposition of α-aminophosphonates

			
k_1	9.40×10^{-4}	2.89×10^{-4}	0.77×10^{-4}

The k_1 rates, i.e. the decomposition of the diester with P-C bond breaking, for the more sterically hindered diisopropyl ester, is three times smaller than that for the diethyl ester. The same conclusion can be drawn from analysis of the diphenyl ester decomposition. It additionally supports the associative mechanism since the dealkylation path is not possible in the last case. Any alternative hydrolysis must go by the same path as the P-C bond breaking via the same or at least a similar pentacoordinate state. Once this state is achieved, the alternative departure of two leaving groups is possible: *O*-phenyl or pyridylaminomethyl anions (probably from different pseudorotamers). The former results in monoester formation via an associative mechanism and the latter is the P-C bond-breaking reaction.

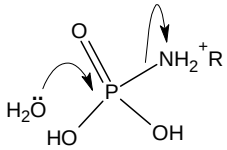
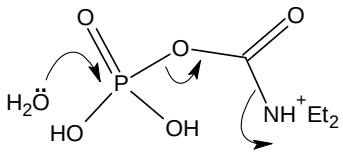
Kinetic isotope effect. The kinetic isotope effect k_H/k_D, equal to 1.02-1.47 for amino phosphonate acids[26] and 2.36-3.17 for aminophosphine oxides[40] was also raised as an argument for the conclusion that P-C bond breaking follows the dissociative mechanism and that the proton attack is involved in the rate limiting stage of the decomposition reaction. The proposed mechanism is shown in Scheme 4.

There is however an alternative explanation of the observed phenomenon. A kinetic isotope effect of k_{H_2O}/k_{D_2O} in the range 2 to 3 is typical for general base catalysis in protolytic reactions and has been found in many bimolecular hydrolysis processes (Table 3).[4,41]

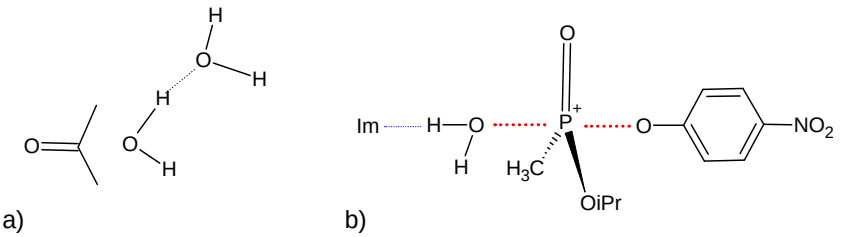


Scheme 4. Dissociative mechanism of α-aminophosphonate decomposition to P^V derivatives.[26]

Table 3. The kinetic isotope effect k_{H2O}/k_{D2O} rate for selected bimolecular reactions in acidic aqueous media[41]

Reaction		k_{H2O}/k_{D2O}
	R = H	1.4
	R= -COPh	1.3
		1.42

Recently a large isotope effect equal to 2.91 and 2.69 was measured for the water- or imidazole-catalyzed attack of water as nucleophile on phosphorus atoms in hydrolyses of phosphonates going via a pentacoordinated transition state (Scheme 5b).[42] The associative mechanism of this reaction was indicated by its high negative entropy ($\Delta S^{\neq}$= -270 and -146 [J/K·mol]).



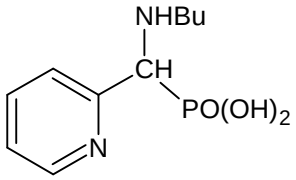
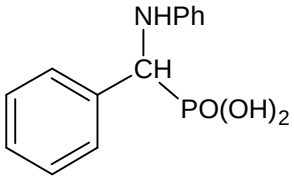
Scheme 5. Water catalyzed hydrolysis and imidazole catalyzed hydrolysis of phosphate esters catalysed by a general base catalysis mechanism.[42]

Thus even the observed high isotope effect 2.36-3.17 in the case of α-aminophoshine oxides[40] does not necessarily support an S_N1@P mechanism and cannot be evidence against the bimolecular S_N2@P process. It rather supports a mechanism proceeding by general base catalysis similar to that presented in Scheme 5a**.**

Thermodynamic studies

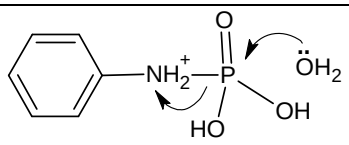
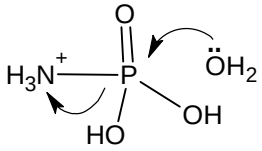
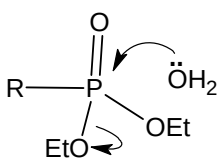
Entropy of activation. Entropy of the reaction is another value that can distinguish between associative and dissociative mechanism. The measured decomposition of 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic phosphonic acid to P^V derivatives has a large negative entropy of activation (-72.4 [J/Kmol]). Entropy values similar to those obtained by us were independently obtained by Boduszek[26] ($\Delta S^{\neq}$= -49.1 and $\Delta S^{\neq}$=-50.3 for 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic acid and 1-(*N*-butylamino)-1-(4-pyridyl)-methylphosphonic acid), however the conditions were not exactly same. It is however important that the entropy of activation in this case is also significantly negative. For comparison, the entropy of activation measured for decomposition of 1-(*N*-phenylamino)-1-phenyl-methylphosphonic acid toward P^{III} products has a large positive value (198.8 [J/K.mol] (Table 4) which is known to be consistent with an elimination process.[24,27,43,44]

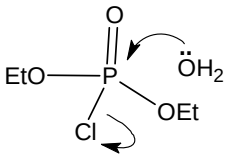
Table 4. The entropy and enthalpy of activation for studied α-aminophosphonate decompositions

	
$\Delta S^{\neq}$= -72,4 [J/K·mol]	**$\Delta S^{\neq}$= 198,8 [J/K·mol]**
$\Delta H^{\neq}$ = 80,0 [kJ/mol]	$\Delta H^{\neq}$ = 168,0 [kJ/mol]

The entropy of activation ΔS of associative reactions in phosphorus chemistry is usually moderately large and negative (from -4 to -130 [J/K·mol]). In the literature one can find many examples supporting this statement (Table 5).

Table 5. Entropy values for selected associative reactions of phosphoroorganic compounds [41]

Reaction		$\Delta S^{\neq}$ [J/K·mol]
	pH 2.3	-52.7
	0.5 M HCl	-88.3
	0.22 M HCl	-59.0
	R= Me	-58.6
	Et	-58.6
	CH_2Cl	-50.2
	Me	-88.3



-92.0

Reactions with dissociative mechanisms usually have large positive values of entropy of activation. Thus the large negative value $\Delta S^{\neq}$= -72.4 [J/K·mol], measured by us for decomposition of 1-(*N*-butylamino)-1-(4-pyridyl)-methylphosphonic acid to *N*-butylaminopyridine and phosphorus P^V compounds suggests the S_N2@P mechanism. Haake and Tyssee[46] who studied acid catalyzed hydrolysis of phosphinanilide suggested that a negative value of entropy (-84 [J/K·mol]) is not necessarily compatible with the S_N2@P mechanism and is not in conflict with an A1 mechanism. They suggested that in such reactions one must consider entropy of protonation. After such a correction, the evaluated value of the entropy of activation for hydrolysis of phosphinanilide was close to 0 eu. On that basis they concluded that the S_N1@P mechanism operated. Later however Harger[13] observed strong sensitivity of this reaction to steric hindrance and concluded that the reaction is consistent rather with the S_N2@P mechanism. His conclusion was supported by other measurements for phosphine amides. Thus the obtained entropy value is not necessarily against, but rather supports, the associative path of decomposition that we have postulated.

In our case the conclusion that decomposition follows an S_N2@P mechanism is strengthened by comparison of the entropy of activation for decomposition of the 1-(phenylamino)-1-phenylmethanephosphonic acid to amine, aldehyde and phosphoric acid III, ($\Delta S^{\neq}$= 198.8 [J/K·mol]) with the entropies of activation for decomposition of 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic acid and 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic acid and 1-(*N*-butylamino)-1-(4-pyridyl)-methylphosphonic acid to amine and phosphoric acid V, ($\Delta S^{\neq}$= -49.1 [J/K·mol][26] (or $\Delta S^{\neq}$= -72.4 [J/K·mol]) and $\Delta S^{\neq}$=-50.3 [J/K·mol][26] respectively (**Table 4**). Entropy of activation for the decomposition of pyridyl- and phenylaminomethylphosphonic acids (cases a and b) differs significantly in absolute value and in sign also. There is no doubt that phenylaminophosphonic acid decomposition follows the S_N1@P mechanism and for it a large positive value is expected. The large negative value for pyridylaminomethanephosphonic acids must then indicate a different mechanism – the substitution process S_N2@P.

Decomposition to P^V *vs* P^{III}, role of the leaving group and amine nitrogen basicity

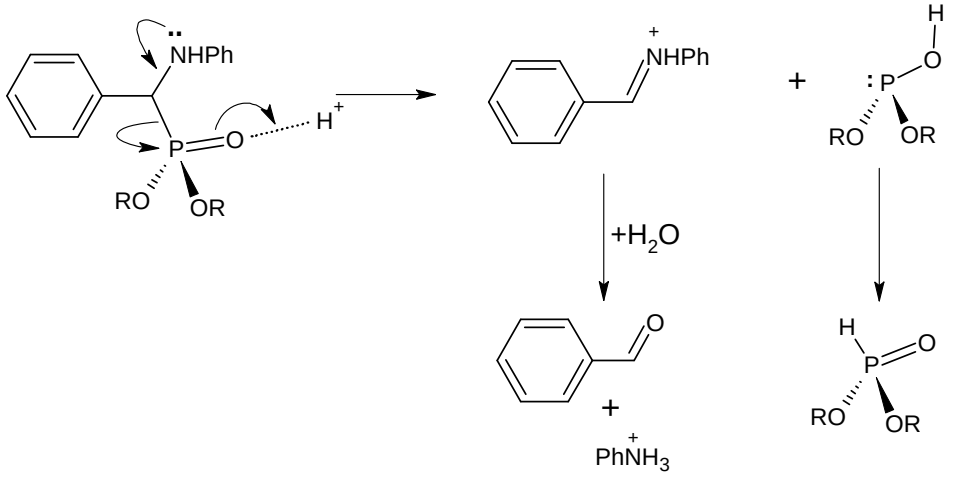
Decomposition to P^{III}. For decomposition of aminophosphonate to P^{III} derivatives.[6,24,27,35,36,43] we have proposed the *retro* Kabachnik elimination mechanism. In this mechanism we assumed that in aminophosphonate (*N*-aromatic, or with bulky groups) the presence of a nitrogen of relatively low basicity causes the equilibrium between species protonated on nitrogen and phosphoryl oxygen to be significantly shifted toward the latter. The nonprotonated amine nitrogen facilitates the next step of the reaction, i.e. P-C bond breaking and formation of the diethyl phosphonate and imine salt as shown in Scheme 6a.

Above we have presented the thermodynamic parameters of that reaction: $\Delta S^{\neq}$= 198,8 [J/K·mol] and $\Delta H^{\neq}$ = 168,00 [kJ/mol]. The highly positive entropy of the reaction is in agreement with the proposed monomolecular mechanism of the decomposition.

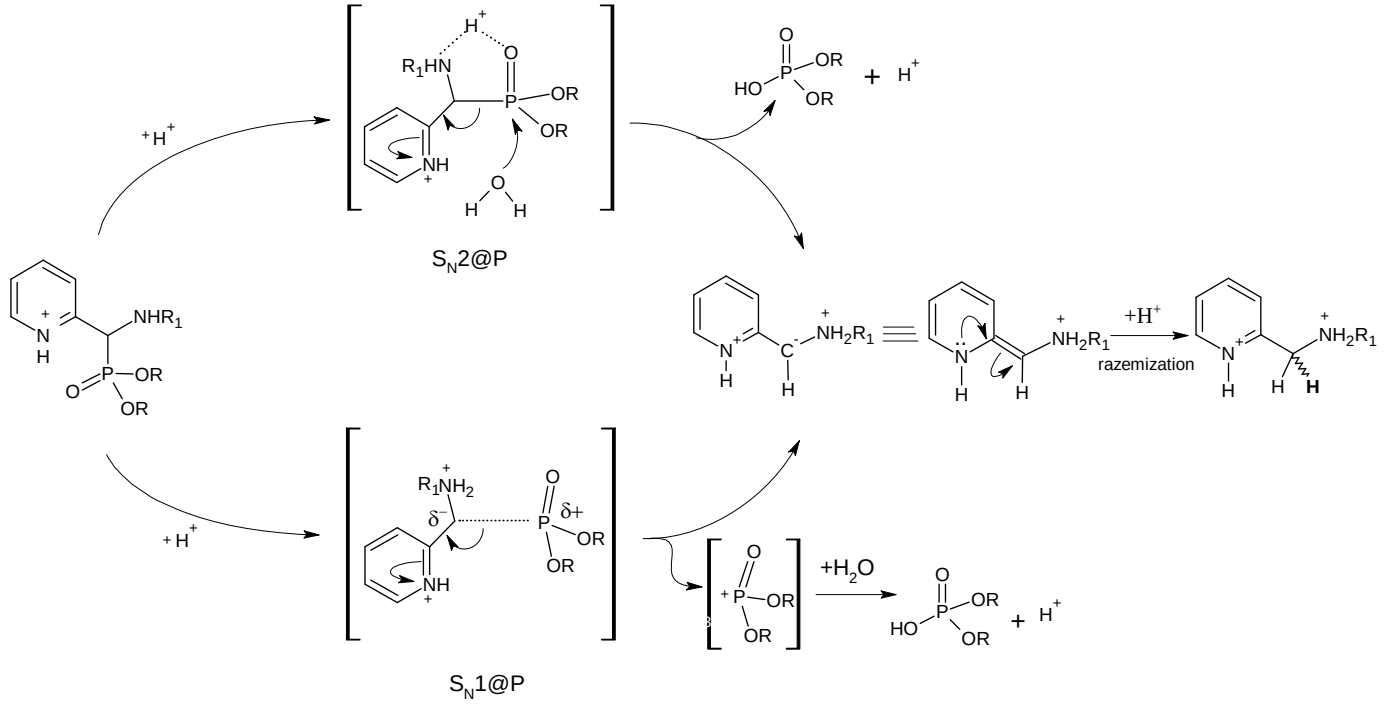
Recently we have analyzed the reaction path on *ab initio* level (B3LYP/6-31G(d,p)). This study confirmed that a three-step process including amino-group protonation, proton transfer through a hydrogen-oxygen bond NH···O(P), [43] and P-C bond cleavage, leading to a protonated imine and derivatives of H-phosphonate is the most probable mechanism.[6,27,28,43,44] It should be noted that for *N*-alkyl aminophosphonates the

decomposition is not observed as the amine nitrogen in this case is protonated and formation of imine (leaving group) is prevented. Lowering the basicity of the amine as is the case in the *N*-benzhydryl derivative, again facilitates the elimination process[47]

Decomposition to P^V. Advanced protonation of the phosphorus oxygen which is postulated in the first step of decomposition of α-aminophosphonates to P^V derivatives makes the phosphorus atom strongly electrophilic[6,35] as described above for the *N*-phenyl phenylaminomethane phosphonates. In this case, nucleophilic attack on the phosphorus electrophilic center and formation of pentacoordinated intermediate or transition state is possible. The presence of a good leaving group attached to a phosphorus atom could lead then to an S_N2@P substitution which results in P-C bond breaking (Scheme 6b upper path). Alternatively the P-C bond could be broken by an S_N1@P process (Scheme 6b lower path). The way the reaction proceeds would depend strongly on the nature of the environment and the presence or absence of a good nucleophile and the presence of a good leaving group.



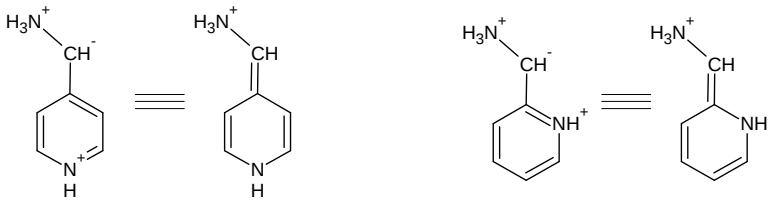
Scheme 6a. The mechanism of α-aminophosphonates decomposition to P^{III} derivatives.



Scheme 6b. Two alternative mechanisms of α-aminophosphonates decompositions toward to P^V derivatives (associative[6,28,43,44]- S_N2@P and dissociative[26] - S_N1@P).

The 2- and 4-pyridylaminomethanephosphonates protonated on pyridine nitrogen posses a good leaving group and only those derivatives, contrary to phenyl and 3-pyridyl derivatives, decompose to a P^V fragment. The structure of the "carbanion like" leaving groups after the P-C bond is broken in the case of 2- and 4-pyridyl derivatives are in fact tautomers of the corresponding amines (Scheme 7). In the case of 3-pyridyl α-aminophosphonates they are not tautomers. It makes these phosphonates stable and of a low tendency for decomposition to P^V derivatives (Scheme 7).

This behavior is common for both mechanisms shown on Scheme 6b since exactly the same leaving group is formed in both cases so it cannot be a factor in distinguishing between either of the presented mechanisms S_N1@P or S_N2@P.[28]



Scheme 7. Mesomeric structures of the possible pyridine leaving groups.

Simultaneous decomposition of pyridyl aminophosphonates to P^{III} and P^V in low acidic media

The 1-*(N*-phenylamino)-1-(2-pyridyl)-methylphosphonic and 1-*(N*-phenylamino)-1-(2-pyridyl)-methylphosphonic acid derivatives possess in their structures both fragments which were discussed as crucial for decomposition to P^{III} (*N*-phenyl) as well as P^V (2- or 4-pyridyl). Depending on the conditions of the reaction, the concentration of aminophosphonate protonated on amine nitrogen can be high or low. It makes them suitable

for both decomposition reactions depending on the pH of the medium. Such behaviour has been indeed observed by us. In low pH when both nitrogens are protonated, the protonated pyridyl fragment forms a good leaving group and the protonated amine nitrogen prevents decomposition to P^{III}. In this case we have observed decomposition exclusively to P^{V} derivatives. When the same compound is heated in low acidity medium such as a mixture of acetic acid and hydrogen chloride solution simultaneous decomposition to both phosphorus III and phosphorus V derivatives was observed. The explanation of this fact is as follows: at high pH the concentrations of the forms that are not protonated on amine nitrogen and not protonated on pyridine nitrogen increase. Both forms facilitate the elimination to P^{III} (increased concentration of non-protonated *N*-phenyl amine nitrogen) and lower the reaction rate of decomposition to P^{V} (decreased concentration of the protonated pyridine nitrogen which is necessary to form a good leaving group).[28,47]

This observation has been reported independently by Boduszek *et al*.[26,45] and by Kiersnowska.[27] In this case the phosphorus III and phosphorus V derivatives are easily distinguished, the former appears in its ^{31}P NMR spectrum in the form of doublets of corresponding multiplicity with a coupling constant $^{1}J_{HP}$ in the range of 680 Hz and with different chemical shift.

Conclusions

The acid catalyzed decomposition of aminophosphonates can lead to P^{III} or P^{V} phosphorus products. The route to P^{III} was found to proceed via an elimination process. It occurs in the cases where there is a relatively low degree of protonation of an amine nitrogen atom. This conclusion about the mechanism is strongly supported by the measured entropy of activation and by theoretical calculations.[37,43,44]

The decomposition to P^{V} derivatives in water was proposed to proceed via nucleophilic substitution, which is typical of compounds containing a tetracoordinated phosphoryl group. Our results – the steric influence on the reaction rate, the low entropy of activation, k_H/k_D typical for bimolecular prototropic reactions, the kinetic studies and the dependence of water concentration on reaction rate – all indicate that nucleophilic substitution or at least advanced formation of a bond with the nucleophile, occur in the transition state. The preliminary calculations also suggest that a bimolecular process is much more probable than the alternative dissociative route. In view of our studies, the postulation of an alternative dissociative mechanism through a three-coordinated metaphosphate-like species is considered not possible in water, but could be observed in non-aqueous media.

Experimental Section

General. 1H (300 MHz) and 31P (120 MHz) NMR spectra were recorded on a Bruker Avance TM DRX (300 MHz) spectrometer. Chemical shifts are reported in parts per million relative to internal tetramethylsilane (Me_4Si, chemical shift=0.0) for 1H NMR.

Diethyl 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonate was prepared according to a known procedure.[45]
The diphenyl and diisopropyl esters of 1-(N-butylamino)-1-(2-pyridyl)-methylphosphonic acid were prepared by the method of reference 42, using diphenyl and diisopropyl phosphite instead of diethyl phosphite. Syntheses of all compounds in Table 1 were performed according to literature procedures.[26,28,45,46]
Diphenyl 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonate: ^{1}H [$CDCl_3$] 8.85 (d, 1H, PyH; $^{3}J_{HH}$ 6.1 Hz), 7.63 (dd, 1H, PyH, ; $^{3}J_{HH} \approx {}^{3}J_{HH} \approx$ 8,2 Hz), 7.48 (d, 1H, PyH, $^{3}J_{HH}$= 8.4 Hz), 6.95 (dd, 1H, PyH; $^{3}J_{HH} \approx {}^{3}J_{HH} \approx$ 6.3 Hz), 7.46-

6.9 (m, 10H, PhH), 4.45 (d, 1H, CH; *J* 21.6), 2.54-2.50 (m, 2H, NCH_2), 1.42-1.35 (m, 2H, NCH_2CH_2), 1.23-1.20 (m, 2H, CH_2CH_3), 0.78 (t, 3H, CH_3CH_2; $^3J_{HH}$ 7.2 Hz). ^{31}P [$CDCl_3$] 16.10.

Diisopropyl 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonate: ^1H [$CDCl_3$] 8.46 (d, 1H, PyH; $^3J_{HH}$ 6.2 Hz), 7.57 (dd, 1H, PyH, ; $^3J_{HH} \approx {}^3J_{HH} \approx 8.4$ Hz), 7.52 (d, 1H, PyH; $^3J_{HH}$ 8.1 Hz), 7.08 (dd, 1H, PyH; $^3J_{HH} \approx {}^3J_{HH} \approx 6.3$ Hz), 4.64-4.45 (m, 2H, $CH(CH_3)_2$), 4.01 (d, CH; $^3J_{HH}$ 18.0Hz), 2.41-2.37 (m, 2H, NCH_2), 1.23-1.13 (m, 6H, $CHCH_3$), 0.97-0.95 (m, 2H,CH_2CH_3), 0.74 (t, CH_3CH_2; $^3J_{HH}$ 7.2 Hz). ^{31}P [$CDCl_3$] 22.32.

Kinetic measurements. The solution of the substrate ($0.2 \cdot 10^{-3}$ mol in 0.6 mL DCl in D_2O solution) was placed in an NMR tube in a thermostat, and the reaction progress was monitored by ^{31}P NMR and $^{31}P\{^1H\}$ NMR. The NMR tube contained coaxial sealed 5-mm NMR tube with 80% H_3PO_4 as reference. The temperature was constant within 0.3 ^oC. At various time intervals the tube was removed from the bath, cooled, and the $^{3|}P$ NMR spectrum recorded. It was found in a separate experiment that reaction in room temperature is very slow so the time when the samples were placed in NMR instrument had no effect on the change of the reactant concentration. The concentrations of the substrate and formed products were determined from the integration of NMR signals. Calculations of the rate constants and the Arrhenius parameters were carried out by the least-squares method. The enthalpy and entropy of activation were calculated for 100 ^oC according to Eyring theory. The concentration of DCl was 20%.

Hydrolysis *vs* dealkylation measurements. $0.20 \cdot 10^{-3}$ mol of the α-aminophosphonate was dissolved in 0.6 mL of 20% solution of DCl in D_2O and the ^1H NMR spectra were recorded at certain time intervals.

Dependence of rate on acidity. The rate of the decomposition was measured by the kinetic method as described above for the series of the sample solution of the DCl in D_2O contain $0.2 \cdot 10^{-3}$ mol of the α-aminophosphonate in 0.6 solvent of DCl in D_2O of different concentration of DCl. The decomposition process was measured by ^{31}P and $^{31}P\{^1H\}$ NMR for about 2 half-lives (70% completion) at 84 ^oC. Calculation of the rate constant was carried out by the least squares method

Chemical shift and ^{31}P signal width as a function of acid concentration. To several tubes with different concentrations of DCl in D_2O the same amount of solution containing of α-aminophosphonate were added to reach a final concentration of $0.2 \cdot 10^{-3}$ mol/dL and the ^{31}P NMR spectra were taken using H_3PO_4 as the external standard.

Thermodynamic activation parameters. Stock solutions of 1-(*N*-butylamino)-1-(2-pyridyl)-methylphosphonic acid and 1-(*N*-phenylamino)-methylphosphonic acid acid were prepared at room temperature by dissolving $0.20 \cdot 10^{-3}$ mol of the corresponding acid in 0.6 mL of 20% DCl in D_2O. The obtained solution was placed in an NMR tube in a thermostated bath. Samples were withdrawn at various intervals. Reactions were followed to at least 95% completion and the concentration of the components of the reaction mixture was measured at certain time intervals and first order rate constants were calculated by root mean square fit. The experiment was performed at three different temperatures: 91, 81, 71 ^oC. Entropy of activation was calculated by fitting to the Eyring equation by plotting ln(k/T) vs 1/T.

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