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# Reactivity of Aminophosphonic Acids. Oxidative Dephosphonylation of 1-Aminoalkylphosphonic Acids by Aqueous Halogens

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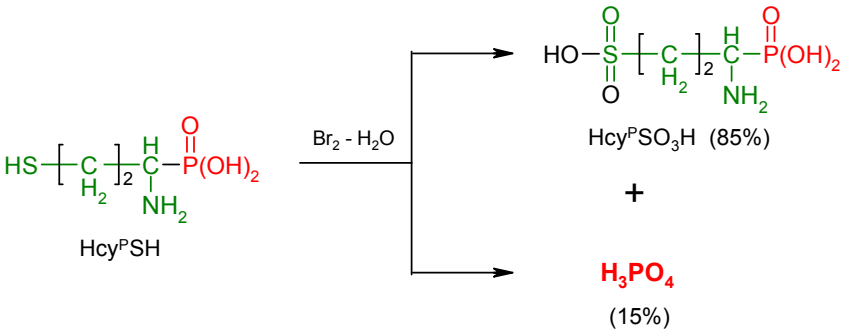
The reactions of 1-aminoalkylphosphonic acids with bromine-water, chlorine-water and iodine-water were investigated. The formation of phosphoric(V) acid, as a result of a halogen-promoted cleavage of the $C_\alpha$-P bond, accompanied by nitrogen release, was observed. The dephosphonylation of 1-aminoalkylphosphonic acids was found to occur quantitatively. In the reactions of 1-aminoalkylphosphonic acids with other halogen-water reagents investigated by $^{31}P$ NMR, scission of the $C_\alpha$-P bond was also observed, the reaction rates being comparable for bromine and chlorine, but much slower for iodine.

## Introduction

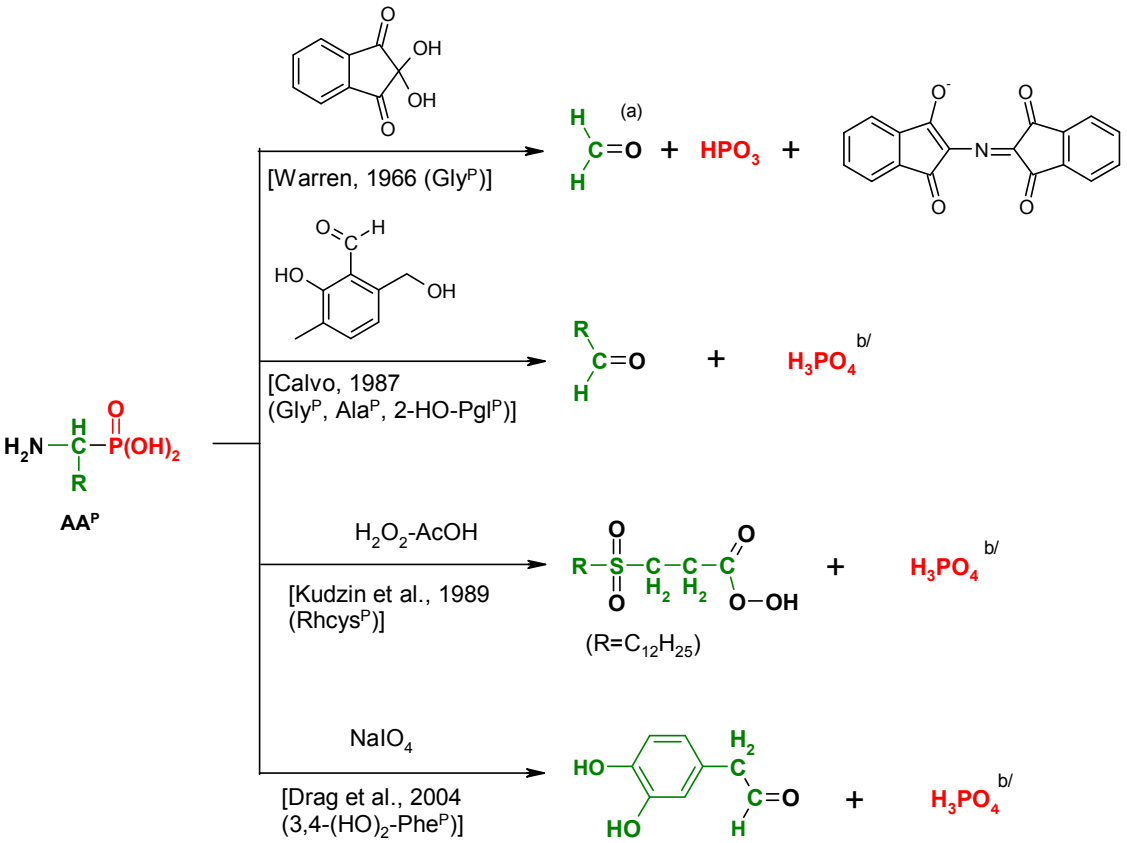
1-Aminoalkylphosphonic acids ($AA^P$) as structural analogues of protein amino acids ($AA^C$), are important inhibitors of enzymes active in amino acid metabolism.[1] Several papers reflected the complexing abilities of the P-C-N class of compounds,[2] and their pharmacological,[3,4] agro-chemical,[5] and industrial applications.[6] Recently several

papers reported the catalytic activity of 1-aminoalkylphosphonates in organic syntheses[7] and physiological interactions.[8] Due to the importance and numerous applications (AA$^P$ were the subject of more than 6000 papers published until 2001),[3] the study of the synthesis of 1-aminoalkylphosphonic acids[9,10] and their derivatives,[11] their biological activity[1,3-5] and physico-chemical properties[12-14] constitute important topics in chemistry and biochemistry.

In 2005 the group at Lodz reported the synthesis of phosphonocysteic and phosphonohomocysteic acids, new phosphonic acid analogues of proteinogenic amino acid metabolites.[15] During that work, it was observed that oxidation of phosphonohomocysteine to phosphonohomocysteic acid (Hcy$^P$SH → Hcy$^P$SO$_3$H) is accompanied by formation of phosphoric acid, resulting from the cleavage of the C-P bond in the parent amino acid (Scheme 1).




**Scheme 1** Oxidation of HcySH$^P$ by aqueous bromine




**Scheme 2** Reactions of 1-aminophosphonic acids resulting in the scission of the P-C bond ([a/]or derivatives of formaldehyde; [b/]in an appropriate ionized form).

This unusual reactivity for the P-C-N compounds was observed earlier only in some reactions of 1-aminophosphonic acids; in the treatment of $AA^P$ with ninhydrin (Warren, 1966),[16] or pyridoxal phosphate (Calvo, 1987),[17] and in the oxidation of 1-amino-3-thiadodecylphosphonic acid by hydrogen peroxide (Kudzin et al., 1989).[18] The dephosphonylation of 1-amino(3,4-dihydroxyphenyl)methylphosphonic acid, during its oxidation with sodium periodate was also reported (Drag et al., 2004)[19] (Scheme 2).

The dephosphonylation of 1-aminophosphonic acid under acidic or basic conditions have also been reported (e.g. Boduszek, 1996, Deron et al., 1999).[20]

In contrast, reports of reactions of carboxylic amino acids ($AA^C$) with halogens, proceeding with simultaneous decarboxylation are more numerous. They are converted to aldehydes (homologous acids) and/or nitriles.[21] More recently this type of reaction of amino acids ($AA^C$) was exhaustively investigated by the Santaballa-Canle group, with both mechanistic and synthetic objectives,[22,23] i.e., as a route to the synthesis of *N*-bromoamino acids – compounds of pharmacological interest.

Since the reaction of aminophosphonic acids with halogenating agents has not been published so far,[24] in this paper we present our findings on the course of the oxidative degradation of 1-aminoalkylphosphonic acids promoted by a bromine-water reagent, a newly explored chemical reaction.

## Results and discussion

### General consideration

The phenomenon of the bromine-promoted dephosphonylation of 1-aminoalkyl-phosphonic acids was observed for the first time for bromine-promoted oxidation of $Hcy^PSH$.[14] Since then, a question on the scope and limitations of this oxidative cleavage of the P-C(N) in $AA^P$ remained.

In order to establish the scope of this reaction, two series of experiments were carried out including:

(i) The reaction of bromine in aqueous solution with representative *C*-phosphonic acids (MPA or PPA), 1-aminoalkylphosphonic acids ($AA^P$: $Gly^P$, $Ala^P$, $Hal^P$, $Val^P$, $Nva^P$, $Nle^P$, $Pgl^P$, $Phe^P$, $Asp^{P,P}$, $Glu^{P,P}$, $Mal^P$ and ACHA, and also 1-(*N*-acetyl-amino)alkylphosphonic acids (Ac-$Gly^P$, Ac-$Ala^P$, Ac-$Pgl^P$ and Bz-$Ala^P$);

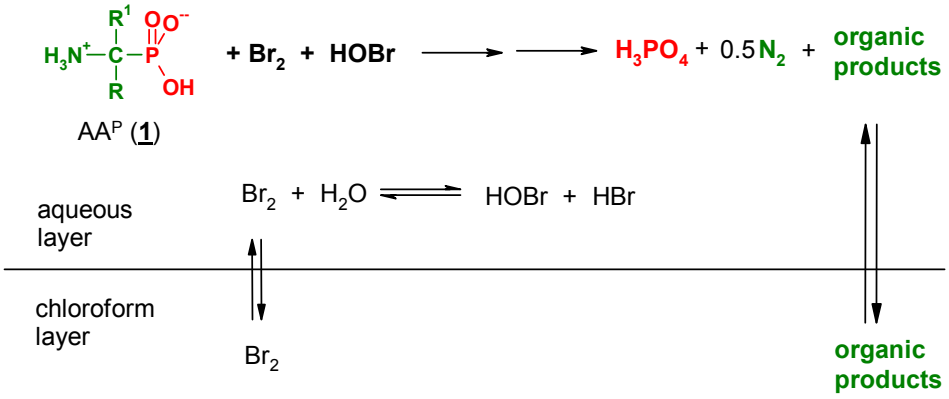
(ii) The reaction of the representative $AA^P$ ($Gly^P$, $Ala^P$, $Mal^P$ and $Pgl^P$) with aqueous chlorine and iodine are also reported.

## Bromine induced dephosphonylation

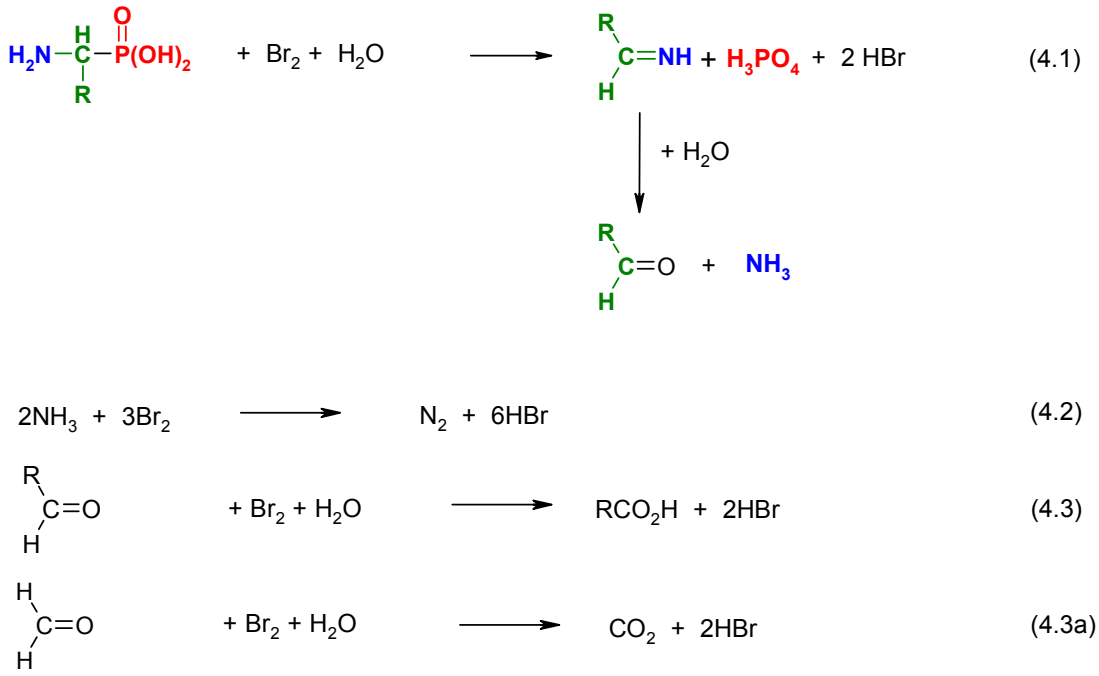
The reactions were carried out, to overcome a low solubility of bromine in water, in a two-phase system consisting of the appropriate aqueous layer [5M HCl, $H_2O$, 2M AcOK/AcOH buffer (pH~4.79)] and an organic (chloroform) layer (Scheme 3).

In a two-phase system, the reactions occurred in the aqueous phase (due to the minimal solubility of $AA^P$ in chloroform). Bromine was continuously supplied by extraction from the chloroform layer, in accord with the extraction coefficients of bromine D [$D_{Br2/(5M\ HClaq/chloroform)}$ = 0.083; $D_{Br2/[water(pH=2.15)/chloroform]}$ = 0.058; $D_{Br2/[buffer(pH=4.5)/chloroform]}$ = 0.058].

The two-phase system used allows the gradual dosing of bromine during the course of the reaction, keeping the bromine concentration in the aqueous phase at a low and relatively constant level. This diminished the rate of the side reaction of bromine with water. At the same time, the dephosphonylated products (and their subsequent further conversions) underwent simultaneous extraction into the organic layer.




**Scheme 3** Scheme of the two-phase reaction system used for investigation of the bromine-promoted dephosphonylation of $AA^P$




**Scheme 4** Consumption of bromine in the exhaustive oxidation of $AA^P$

We are assuming that the bromine-promoted dephosphonylation of 1-aminoalkyl-phosphonic acids proceeds via three major steps of oxidation:

(i) Spliting of the C-P bond of $AA^P$ with simultaneous formation of the corresponding imines (Scheme 4.1);

(ii) Oxidation of the ammonia released to nitrogen (Scheme 4.2);

(iii) Subsequent oxidation of the aldehyde intermediate formed to carboxylic acids (Scheme 4.3).

These afford the quantitative stoichiometry of $AA^P$:$Br_2$=1:1 (Scheme 4.1) for $Mal^P$, $AA^P$:$Br_2$=1:2 for $Ala^P$, $Pgl^P$, etc. (Schemes 4.1 & 4.3) and $AA^P$:$Br_2$=1:3 for $Gly^P$ (Scheme 4.1 & 4.3a).

Taking into account the oxidation of ammonia to nitrogen (Scheme 4.2), the total stoichiometry of $AA^P$:$Br_2$ equals: $Mal^P$:$Br_2$=1:2.5, $Ala^P$:$Br_2$=1:3.5; $Gly^P$:$Br_2$=1:4.5. For

practical reasons, however, a stoichiometry $AA^P$:$Br_2$ of 1:5 has been used throughout the work.

The results on oxidative dephosphonylation of the representative phosphonic acids are illustrated in Table1 and presented schematically in Fig. 1.

**Table 1** Results of $^{31}P$ NMR analysis of aqueous layers of the two-phase reaction mixtures of $AA^P$ (0.5 mmol)/aq. layer (2.5 ml)/$Br_2$ (2.5 mmol)/$CHCl_3$ (2.5 ml) recorded after 0.1h of reaction (25 $^oC$ ±0.5 $^oC$)

| $AA^{P/a}$ | $Gly^P$ | | | | | | $Ala^P$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aq. layer | Water[/b] | | 5M HClaq | | Buffer[/c] | | Water[/c] | | 5M HClaq | | Buffer[/c] | |
| δ ($^{31}P$) ppm | $Gly^P$ | Pi | $Gly^P$ | Pi | $Gly^P$ | Pi | $Ala^P$ | Pi | $Ala^P$ | Pi | $Ala^P$ | Pi |
| | 13.9 | -1.2 | 13.9 | -1.2 | 13.9 | -1.2 | 16.8 | -1.2 | 16.8 | -1.2 | 16.8 | -1.2 |
| RA[/b] [%] | 86 | 14 | 100 | 0 | 0 | 100 | 90 | 10 | 100 | 0 | 0 | 100 |
| $AA^{P/a}$ | $Mal^P$ | | | | | | $Pgl^P$ | | | | | |
| Aq. layer | Water[/c] | | 5M HClaq | | Buffer[/c] | | Water[/c] | | 5M HClaq | | Buffer[/c] | |
| δ ($^{31}P$) ppm | $Mal^P$ | Pi | $Mal^P$ | Pi | $Mal^P$ | Pi | $Pgl^P$ | Pi | $Pgl^P$ | Pi | $Pgl^P$ | Pi |
| | 19.2 | -1.2 | 19.2 | -1.2 | 19.2 | -1.2 | 12.5 | -1.2 | 12.5 | -1.2 | 12.5 | -1.2 |
| RA[/b] [%] | 48 | 52 | 100 | 0 | 0 | 100 | 64 | 36 | 100 | 0 | 0 | 100 |

[a/]The structures of $AA^P$ used are given in Supporting Information. [b/]RA – Relative integrated areas of $^{31}P$ signals. [b/]In case of the reactions monitored for $AA^P/Br_2/H_2O/CHCl_3$ and $AA^P/Br_2/H_2O$ (buffer)/$CHCl_3$ - $^{31}P$ NMR spectra were recorded after prior acidification of the samples to approximately 5M HCl.

**Fig. 1** $^{31}$P NMR monitoring of aqueous layers of the two-phase reaction mixtures of Gly$^{P}$ (0.5 mmol) and the bromine/water reagent (2.5 mmol), carried out at 25 $^{o}$C (±0.5 $^{o}$C) for the indicated solvent systems:

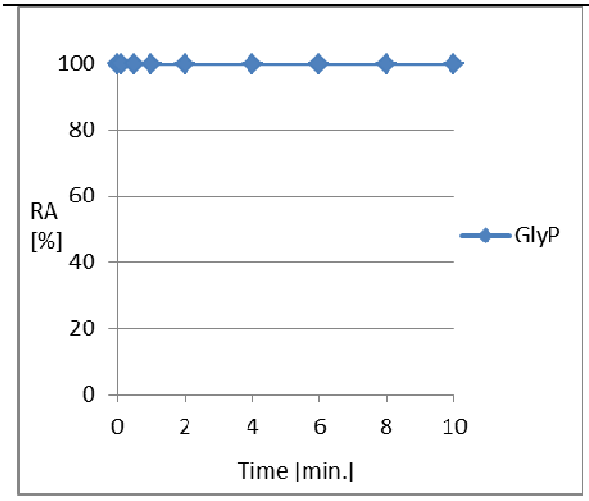



**Fig. 1.1** Gly$^{P}$/$Br_2$/$H_2O$ (5M $HCl_{aq}$)/$CHCl_3$ (2.5 mL: 2.5 mL)

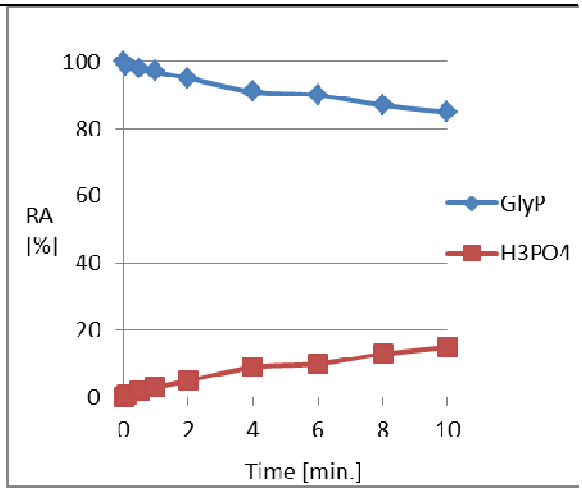



**Fig. 1.2**Gly$^{P}$/$Br_2$/$H_2O$/$CHCl_3$ (2.5 mL: 2.5 mL)

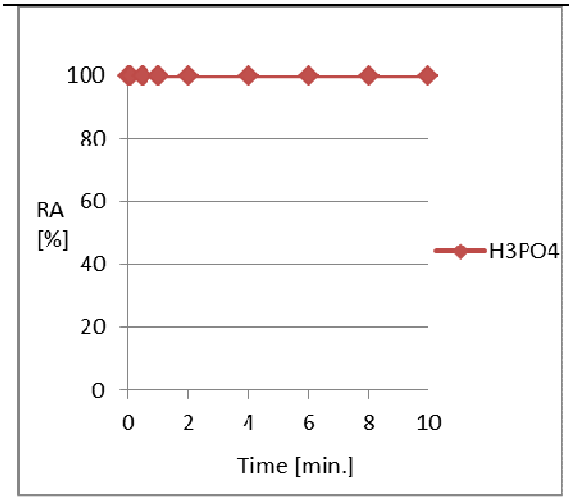



**Fig. 1.3** Gly$^{P}$/$Br_2$/$H_2O$ (buffer)/$CHCl_3$ (2.5 mL: 2.5 mL)

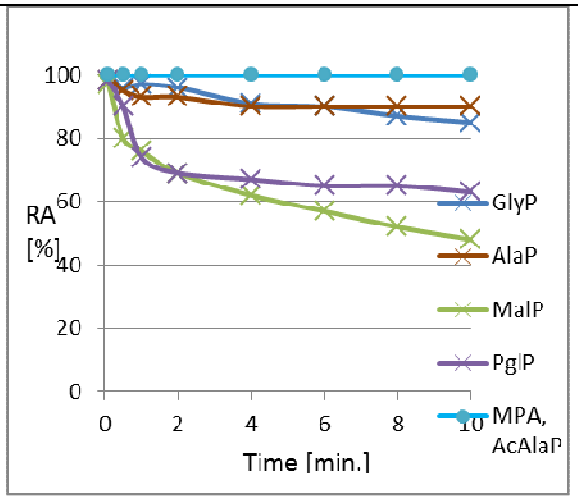



**Fig. 1.4** PA (AA$^{P}$, MPA, Ac-AA$^{P}$)/$Br_2$/$H_2O$/$CHCl_3$ (2.5 mL: 2.5 mL)

For the reactions monitored for AA$^{P}$/$Br_2$/$H_2O$/$CHCl_3$ and AA$^{P}$/$Br_2$/$H_2O$ (buffer)/$CHCl_3$ - the $^{31}$P NMR spectra were recorded after prior acidification (to *ca*. 5M HCl) of the samples.

The results revealed that the dephosphonylation of all AA$^{P}$ examined fails to occur in 5M HCl solutions, even during a prolonged reaction time (over 200 h). These

findings are in accord with our earlier observation on the quantitative course of oxidation of $HCy^{P}SH$ to $HCy^{P}SO_3H$ in 5M HCl solutions.[14]

Subsequently, we found that acidification of the reaction mixtures to 5M HCl (resulting in protonation of the amino group) is a convenient way of quenching the bromine-promoted dephosphonylation of 1-aminoalkylphosphonic acids at the appropriate time. $^{31}P$ NMR analysis of both phases of the reaction system revealed the presence of $H_3PO_4$ as the final phosphorus product in the aqueous phase, and the absence of any phosphorus-containing compounds in the chloroform phase. Reactions carried out in a buffer solution (pH~4.79) started immediately and proceeded with evolution of a colorless neutral gas (test with a wet indicator paper), presumably nitrogen. Alkalinization of aliquot samples revealed the absence of ammonium ions in the aqueous layer.

In mildly acidic aqueous solutions (acetate buffer solution; pH=4.79) the dephosphonylation of 1-aminoalkylphosphonic acids occurred quantitatively, but with a moderate rate in water, with a trend of a decreasing rate as the pH of the aqueous phase decreased from an initial pH<2.15 to ~0.5 during the reaction.

The hypothesized three-step mechanism of the bromine-promoted dephosphonylation of $AA^{P}$ is presented in Scheme 4.

Iodometric determination of the unconsumed bromine in the reaction mixtures also revealed that much less bromine (1 to 2 equivalents) is required for complete reaction of 1-aminoalkylphosphonic acids (Fig. 2).

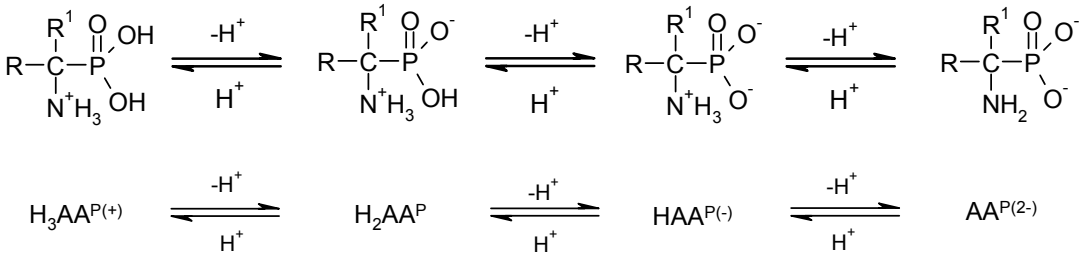
The results revealed:

i) Fast and quantitative dephosphonylation of $AA^{P}$ in buffer solutions and partial dephosphonylation in aqueous solutions;

ii) Total inertness of C-phosphonic acids and Ac-$AA^P$ in aqueous and buffer solutions;

iii) Total inertness of $AA^P$ in 5M HCl solutions, suggesting the key role of the free amine function in the reaction.

We have found that the rates of the bromine-promoted dephosphonylation of 1-aminoalkylphosphonic acids in water depend on the structure of the $AA^P$ used (Fig. 1.4.), which directly influences the protonation of the amino group (Scheme 5), and secondly, on the stoichiometry of the bromine consumption (accompanied by the equivalent release of HBr) in the prolonged oxidation of the aminoalkyl part of the $AA^P$ moiety (Scheme 4).




**Scheme 5** Dissociation/protonation equilibrium of $AA^P$ (Results of the determination of the protonation/dissociation equilibria of $AA^P$ are supplied in the Supporting Information).

## Bromine induced dephosphonylation – the rate of bromine consumption

The profiles of bromine consumption during the 1h two-phase reaction of bromine with $AA^P$ ($Ala^P$ and $Hal^P$), and estimated products of the $AA^P$ dephosphonylation (Scheme 4.1), namely, ammonium bromide and propanal ($Hal^P$) are presented in Fig. 2.

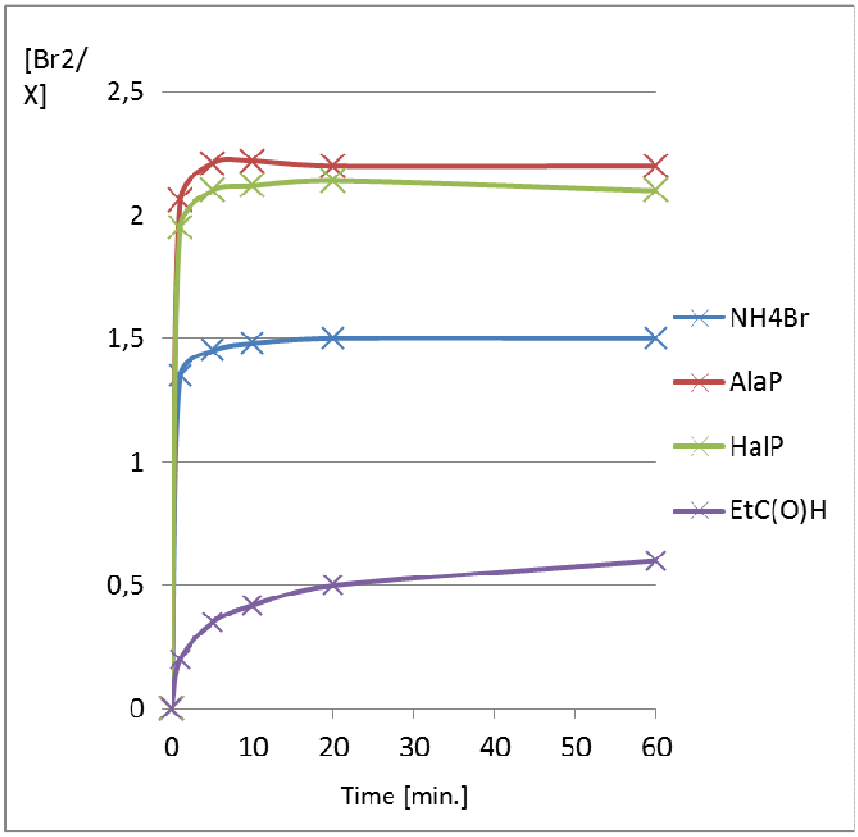


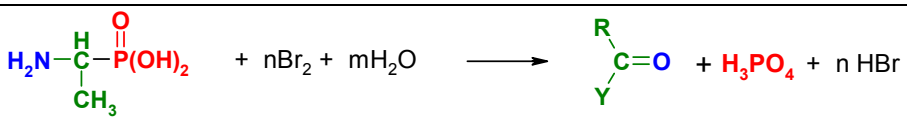

**Fig. 2** The profile of bromine consumption in reaction with $AA^P$ ($Ala^P$ and $Hal^P$), ammonium bromide and propanal.

These data suggest that the reaction of bromine and $AA^P$ ($Ala^P$ or $Hal^P$) consumes over 2 mmol of bromine per mmol of $AA^P$ in the initial phase of the reaction (1-5 min), with a plateau in the period of 5-60 min. In the same reaction time ammonium bromide consumes nearly 1.5 equivalents of bromine with a plateau in the period of 5-60 min, whereas aldehyde consumes only 0.4 mmoles of bromine in the period of 1-5 min, 0.5 mmoles of bromine after 20 min with a further slow increase of bromine consumption up to 1 equivalent (Scheme 4.3) over the longer time.

These data correspond to the set of $^{31}P$ NMR experiments for the reaction of $Ala^P$ and bromine carried out for the stoichiometry of $Ala^P$:$Br_2$=1:1 (0.25 mmol:0.25 mmol);

1:2 (0.25 mmol:0.50 mmol); 1:3 (0.25 mmol:0.75 mmol) and 1:4 (0.25 mmol:1.0 mmol). The corresponding $^{31}$P NMR spectral results are summarized in Table 2.

**Table 2** Products of the bromine induced dephosphonylation of $Ala^P$ at different molar ratios of $Ala^P$:$Br_2$




| $^{31}$P NMR | $Ala^P$:$Br_2$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $Ala^P$:$Br_2$=1:1 | | $Ala^P$:$Br_2$=1:2 | | $Ala^P$:$Br_2$=1:3 | | $Ala^P$:$Br_2$=1:4 | |
| δ($^{31}$P) [ppm] | $Ala^P$ | $P_i$ | $Ala^P$ | $P_i$ | $Ala^P$ | $P_i$ | $Ala^P$ | $P_i$ |
| | 14.1 | 0.1 | 14.1 | 0.1 | 14.1 | 0.1 | 14.1 | 0.1 |
| RA [%] | 27.8 | 69.4 | 0 | 100 | 0 | 100 | 0 | 100 |

$^{31}$P NMR spectra were recorded after 10 min. of reaction time. $P_i$– $K_{3-i}H_iPO_4$ (i=0-3).

Recapitulating, the dephosphonylation of $AA^P$ (scission of the P-C bond in $AA^P$) requires only 1 equivalent of bromine. However, this reaction is accompanied by a subsequent quick oxidation of released ammonia (imine nitrogen) which consumes 1.5 equivalent of bromine (Scheme 4.2; Fig. 2) and the subsequent slow oxidation of aldehyde (up to 1 equivalent of bromine in a prolonged reaction period) (Scheme 4.3; Fig. 2).

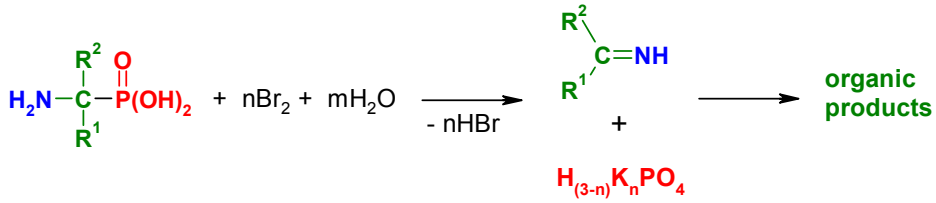
## Identification of dephosphonylation products

In order to identify the organic products of the bromine-promoted dephosphonylation of 1-aminoalkylphosphonic acids, these reactions were run using an aqueous solution of $AA^P$ buffered with acetic acid/potassium acetate. The organic products of dephosphonylation were continuously extracted into the chloroform layer during the

reaction, and, after the usual work-up (see Experimental), they were analyzed by GC-MS (Table 3).

Additional direct proof for the formation of carbonyl products by bromine from the dephosphonylation of $AA^P$ was given by their isolation from the reaction mixtures as the corresponding 2,4-dinitrophenylhydrazones (see Supporting Information).

**Table 3** GC-MS analysis of organic products of the dephosphonylation of $AA^P$ (DB-1 column)




| | | | Volatile organic products of $AA^P$ dephosphonylation (relative contents [%] in organic phase)[a] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $R-C(=O)-Y$ | | | | | |
| $AA^P$ | R | $R^1$ | $Y=R^1$ | Y=OH | $Y=NH_2$ | R-CN | Aldol [b,c] | Imine | Others ident. [d,e] |
| $Nle^P$ | Bu | H | 29. | 10. | 5. | 10. | 7.[b] | 30. | |
| $Pgl^P$ | Ph | H | 70. | 6. | 5. | 11. | | | |
| $Phe^P$ | Bn | H | 32. | | | 29. | 6.[c] | | 26.[d] |
| $ACHPA^P$ | $(CH_2)_5$ | | 60. | | | | | 10. | 12.[e] |

[a/]Determined on the basis of relative surface area of appropriate chromatogram peaks. [b,c/]Dehydrated aldols: [b/][154] and [c/][212]. [d,e/]Other identified compounds: [d/]BnBr [171] and [e/]Cyclohexanone×$Br_2$ [256] (see Supporting Information).

## Reaction of $AA^P$ with other aqueous halogen reagents

Representative $^{31}P$ NMR spectral results of the reaction mixtures of $AA^P$ ($Gly^P$, $Ala^P$, $Hal^P$ and $Pgl^P$) with chlorine - $AA^P$/aq. buffer/$Cl_2$/$CHCl_3$ are presented in Table 4. The corresponding $^{31}P$ NMR spectra recorded after 5-10 min. of reaction time exhibit quantitative dephosphonylation of the $AA^P$ being investigated.

**Table 4** Contents of the reaction mixture for reactions of $AA^P$ (0.25 mmol) with chlorine/hypochloric acid (1 mmol) (in $CHCl_3$/2M AcOK aq.), determined after 10 min. (25 °C ±0.5 °C)

| $AA^P$ | $Gly^P$ | | | $Ala^P$ | | | $Mal^P$ | | | $Pgl^P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| δ ($^{31}P$)$^{/a}$ ppm | $Gly^P$ | $P_i^{/a}$ | $PP_i^{/a}$ | $Ala^P$ | $P_i^{/a}$ | $PP_i^{/a}$ | $Mal^P$ | $P_i^{/a}$ | $PP_i^{/a}$ | $Pgl^P$ | $P_i^{/a}$ | $PP_i^{/a}$ |
| | 10.5 | 1.1 | -1.7 | 13.8 | 1.2 | -1.7 | 16.5 | 1.2 | -1.7 | 10.4 | 1.2 | -1.7 |
| $RA^b$ [%] | 0 | 94 | 6. | 0 | 95 | 5. | 0 | 93 | 7. | 0 | 97 | 3. |

[a/] $P_i$: $K_{3-i}H_i PO_4$ (i=0-3); $PP_i$: $K_{4-j}H_jP_2O_7$ (j=0-4). [b]RA: Relative integrated areas of $^{31}P$ signals.

Representative $^{31}P$ NMR spectral results of the reaction mixtures of $AA^P$ ($Gly^P$, $Ala^P$, $Hal^P$ and $Pgl^P$) with iodine -$AA^P$/aq buffer/$I_2$/$CHCl_3$ are presented in Table 5. The corresponding spectra recorded after 1h exhibit no traces of $H_3PO_4$, while recorded after 72h exhibited variable amounts of $H_3PO_4$ ($Gly^P$ - 0%; $Ala^P$ - *ca*. 3.%; $Mal^P$ - *ca*. 6%; $Pgl^P$ - *ca*. 30%).

**Table 5** Contents of the reaction mixture for reactions of $AA^P$ (0.25 mmol) with iodine, determined after 72h (25 °C ±0.5 °C)

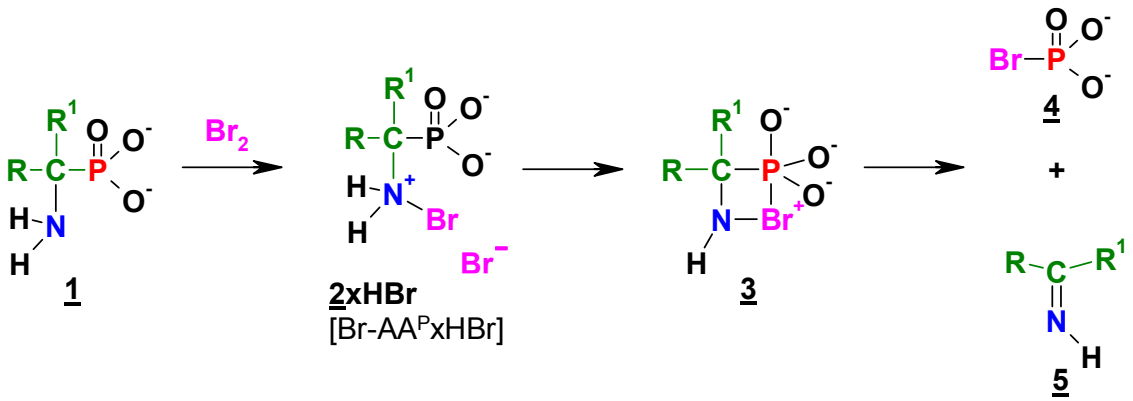
| $AA^P$ | | $Gly^P$ | | $Ala^P$ | | $Mal^{P/a}$ | | $Pgl^{P/a}$ | |
|---|---|---|---|---|---|---|---|---|---|
| P-Comp. | | $Gly^P$ | $P_i$ | $Ala^P$ | $P_i$ | $Mal^P$ | $P_i$ | $Pgl^P$ | $P_i$ |
| ppm | | 10.42 | 0.22 | 13.8 | 0.22 | 16.6 | 0.21 | 13.8 | 0.22 |
| | | | | Reaction time | | | | | |
| 1h | % | 100 | 0 | 100 | 0 | 100 | 0 | 100 | 0 |
| 72h | % | 100 | 0 | 96.6 | 3.4 | 94.0 | 6.0 | 70.0 | 30.0 |

[a/] $P_i$: $K_{3-i}H_i PO_4$ (i=0-3)

## Reaction course

The results in Table 3 indicate that the major products are aldehydes (or ketones in case of Mal$^P$ and ACHPA). Carboxylic acids, nitriles (absent in case of Mal$^P$ and ACHPA), amides and/or aldol condensation products are present only as minor products. However, the relative yields of the organic products of the dephosphonylation, namely carbonyls **5A**, acids **5B**, amides **5C**, and nitriles **5D**, were found to be dependent on the structure of the starting AA$^P$, and also on the reaction conditions used (e.g., excess of bromine and reaction time).

These experimental findings, consistent with the chlorine-promoted mechanism of decarboxylation of α-amino acids described by Armesto et al.,[22,23] allow us to postulate a mechanism of the bromine-promoted dephosphonylation of 1-aminoalkyl-phosphonic acids (Scheme 6).



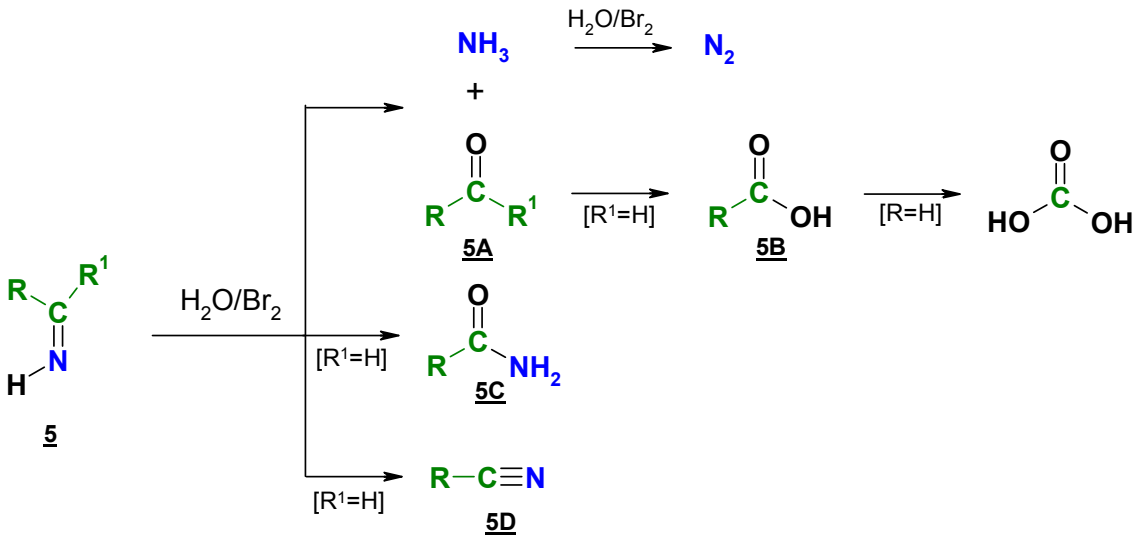

Corrected version

**Scheme 6** Postulated mechanism of the 1-AA$^P$ dephosphonylation

This mechanism assumes the initial *N*-bromination of 1-aminoalkyl-phosphonates to the corresponding *N*-bromoaminoalkylphosphonates (**2**) in the first stage (AA$^P$→Br-AA$^P$; **1**→**2**) (similarly to the reaction of α-amino acids [Armesto et al.,

1993][22]), followed by a rapid rearrangement of the Br-AA$^P$ formed (**2**) to the cyclic pentacoordinated phosphorus intermediate **3** (**2**→**3**)[25] in the second stage.

This mechanism, requiring one mole of bromine per mole of AA$^P$ (such a stoichiometry of the bromine-AA$^P$ reaction was established by determination of the bromine consumption using iodometric titration of both phases of the reaction system), is entirely different from the mechanistic paths proposed for *N*-haloamino acids by Armesto.[22] The intermediate **3** decomposes rapidly by rupture of the C-P bond with the simultaneous formation of two unstable intermediates: bromophosphate **4** – hydrolyzing immediately to phosphoric acid; and imine **5** – the latter hydrolyzing to carbonyls and ammonia. The imine is the precursor for a variety of observed products, i.e., carbonyl compounds **5A**, acids **5B**, amides **5C**, and nitriles **5D** (Scheme 7).




**Scheme 7** Conversions of the imine intermediate **5** to carbonyl compounds **5A**, carboxylic acids **5B**, carboxamides **5C** and/or nitriles **5D**

According to this mechanism, the observed evolution of nitrogen during the reaction is caused by the simultaneous bromine induced oxidation of the ammonia/ammonium ion released during the hydrolysis of imines **5** (Scheme 4.3).

## Conclusions

In summary, we have described the unusual dephosphonylation reaction of 1-aminoalkylphosphonic acids during their reaction with bromine. This reaction occurs by chemical cleavage of the C-P bond of 1-$AA^P$, presumably via formation of *N*-bromo-aminoalkylphosphonic acid ($AA^P \rightarrow$Br-$AA^P$; **1**→**2**) in the first stage, its rearrangement to a pentacoordinate phosphorus intermediate (**2**→**3**) in the second stage, followed by rupture of its P-C bond. Simultaneously, bromophosphoric acid is released, hydrolyzing rapidly to phosphoric acid in the final step. The reaction was found to be dependent on the pH of the solution. The organic products formed during the dephosphonylation were mainly carboxylic acids and the corresponding amides and/or nitriles.

In the reactions of 1-aminoalkylphosphonic acids with other halogen-water reagents investigated by $^{31}$P NMR, scission of the $C_\alpha$-P bond was also observed, with reaction rates comparable for bromine and chlorine, and substantially slower for iodine.

## Experimental

### Synthesis of starting materials

1-Aminoalkylphosphonic acids: phosphonoalanine ($Ala^P$); phosphonohomoalanine ($Hal^P$); phosphonovaline ($Val^P$); phosphononorvaline ($Nva^P$); phosphononorleucine

(Nle$^{P}$); phosphonophenylglycine (Pgl$^{P}$) and phosphonophenylalanine (Phe$^{P}$), were prepared and purified according to Kudzin & Stec.[10] Phosphonoglycine (Gly$^{P}$), 1-amino-1-methylethylphosphonic acid (Mal$^{P}$) and 1-aminocyclohexyl-1-phosphonic acid (ACHPA) were prepared according to Soroka.[26] 1-Aminoethyl-1,2-diphosphonic acid (Asp$^{P,P}$) and 1-aminopropyl-1,3-diphosphonic acid (Glu$^{P,P}$) were synthesized according to the Ref. Kudzin & Majchrzak,[26(a)] and Kudzin et al.,[26(b)] respectively. 1-(*N*-Acetylamino)ethyl-1-phosphonic acid (Ac-Ala$^{P}$) and 1-(*N*-acetylamino)-phenylmethyl-1-phosphonic acid (Ac-Pgly$^{P}$) were synthesized according to the Ref. Kudzin at al., 2005.[14] Methylphosphonic acid (MPA) and phenylphosphonic acid (PPA), and other reagents were purchased from Aldrich (Milwaukee, Ill., USA).

(Abbreviations of AA$^{P}$ follow the general rules elaborated by Kudzin et al.[10, 28])

## Reaction of phosphonic acids with a halogen/water reagent

### Examination of the rate of bromine induced dephosphonylation

A sample (0.20 mmol) of phosphonic acid [AA$^{P}$, Ac-AA$^{P}$ or PA] was dissolved in 2.5 mL of water (A), or in 2M aq. acetate buffer (pH 4.79) (B) or 5M aq. HCl (C). To the solution of phosphonic acid 1M solution of bromine in chloroform (2.5 mL) was added, and the reaction mixture was vigorously stirred at 25 $^{o}$C (±0.5 $^{o}$C) for the reported period of time. For the $^{31}$P NMR measurements, aliquots of aqueous layer (0.25 mL) were removed (experiments A and B) and were acidified with 10M aq.HCl to ca. 5M HCl (0.25 mL), then $D_2O$ (0.1 mL) was added. For $^{31}$P NMR measurements for experiment C, 0.25 mL aliquots were removed to which $D_2O$ (0.25 mL) was added and spectra were recorded without prior acidification.

### Determination of the rate of chlorine induced dephosphonylation

The phosphonic acid [$AA^P$: $Gly^P$, $Ala^P$, $Mal^P$ and $Pgl^P$; 0.20 mmol] was dissolved in 10M aq. solution of KOH (0.2 mL; 2 mmol) and acidified with AcOH (0.40 mL; 0.42 g; 7.0 mmol). To this solution was added chloroform (1.3 mL) and during vigorous stirring a solution of 1.4M aq. NaClO (0.7 ml) was gradually added in 1 min. The reaction mixture was vigorously stirred at 25 $^oC$ (±0.5 $^oC$) for the reported period of time. To the aliquots removed from the aqueous layer (0.3 mL) was added 0.02M aq. EDTA (0.1 mL) and $D_2O$ (0.1 mL) before recording the $^{31}P$ NMR spectra.

### Determination of the rate of iodine induced dephosphonylation

The phosphonic acid [$AA^P$: $Gly^P$, $Ala^P$, $Mal^P$ and $Pgl^P$; 0.20 mmol] was dissolved in 10M aq. solution of KOH (0.3 mL; 3 mmol), then diluted with water (0.3 mL) and neutralized by addition of AcOH (0.30 mL; 0.31 g; 5.2 mmol). This solution was allowed to stand for 24h, centrifuged if necessary, and enriched with solid iodine (0.254 g; 1 mmol), followed by chloroform (1.3 mL). The reaction mixture was stirred at 25 $^oC$ (±0.5 $^oC$) for the reported period of time. To the aliquots removed from the aqueous layer (0.3 mL) was added 0.02M aq. EDTA (0.1 mL) and $D_2O$ (0.1 mL) before recording the $^{31}P$ NMR spectra.

## Determination of bromine consumption

### Determination of bromine consumption using $^{31}P$ NMR

Samples of $Ala^P$ (0.25 mmol) were placed into 25 mL Erlenmayer flasks and dissolved in 2M aq. acetate buffer (pH 4.79, 1 mL). To the resulting solutions appropriate amounts of bromine (0.25, 0.50, 0.75 or 1 mmol) in chloroform (1 mL) was added and the two-phase reaction mixtures were vigorously stirred (in the dark at 25 $^oC$) for a predetermined time. To the aliquots removed from the aqueous layer

(0.3 mL) was added 0.02M aq. EDTA (0.1 mL) and $D_2O$ (0.1 mL) before recording the $^{31}P$ NMR spectra.

**Determination of bromine consumption using iodometric titration**

A sample of individual $AA^P$ (0.20 mmol) was placed into a 25 mL Erlenmayer flask and dissolved in 2M aq. acetate buffer (pH 4.79, 1 mL). To the resulting solution 1M solution of bromine in chloroform (1 mL) was added and the two-phase reaction mixture was vigorously stirred (in the dark at 25 $^oC$) for a predetermined time. To the reaction mixture 1M aq. KI (1mL), followed by 4M aq. $H_2SO_4$ (10 mL) were added and the reaction mixture was vigorously stirred in the dark, at ambient temperature, for 15 min. Next, the iodine released was titrated using 0.2M aq. $Na_2S_2O_3$. At the end of titration one drop of a 1% starch indicator was added.

Determination of bromine consumption in the reaction with ammonium bromide, or aldehydes (propanal) using iodometric titration, was carried out in a manner identical to that described for $AA^P$.

**The extraction coefficient of bromine D –** was determined by iodometric titration of bromine in the appropriate separated phases.

## Analysis of products of dephosphonylation

**GC-MS analysis of organic products of $AA^P$ dephosphonylation**

A sample of $AA^P$ (0.20 mmol) was dissolved in 2M aq. acetate buffer, (pH 4.79, 2.5 mL), and to the resulting, well stirred solution 1M solution of bromine in chloroform (2.5 mL) was added. The two-phase reaction mixture was stirred at 25 $^oC$ for 30 min, and the layers were separated. The chloroform layer was purged with argon until

decolorized, extracted with water (2×5 mL) and dried over anh. $Na_2SO_4$. These samples were subjected to GC-MS analysis.

**Identification of carbonyl products resulting from $AA^P$ dephosphonylation as their 2,4-dinitrophenylhydrazones**

A sample of $AA^P$ (0.20 mmol) was dissolved in 2M aq. acetate buffer (pH 4.79, 2.5 mL), and to the resulting well-stirred solution, 1M bromine in chloroform (2.5 mL) was added. The two-phase reaction mixture was stirred at 25 $^oC$ for 30 min, the layers were separated and the chloroform layer was purged with argon until decolorized. This solution was dropped into 0.05M solution of 2,4-dinitrophenylhydrazine (3 mL) and the reaction mixture was left for 24h. The precipitated 2,4-dinitrophenylhydrazones were isolated by decanting, recrystallized from ethanol (1mL, 96%) and dried under vacuum.

## $^{31}P$ NMR analysis of $AA^P$ dephosphonylation products

A sample of $AA^P$ (0.20 mmol) was dissolved in 2M aq. acetate buffer, (pH 4.79, 2.5 mL), and to the resulting stirred solution, 1M bromine in chloroform (2.5 mL) was added. The reaction mixture was stirred at 25 $^oC$ for 30 min, and the layers were separated. The chloroform layer (*ca*. 2 mL) was divided into two equal fractions (*ca*. 2×1 mL). The first fraction was mixed with 2M aq. KOH (1 mL) and the formed two-phase system was purged with argon to homogenization. The second fraction was mixed with 0.1M solution of MPA (internal standard) in 2M aq. KOH [MPA: $\delta(^{31}P)_{2M\ KOH}$=20.3 ppm] (1 mL) and the two-phase system formed was purged with argon to homogenization. To the samples (0.3 mL) was added 0.02M aq. EDTA (0.1 mL) and $D_2O$ (0.1 mL) before recording the $^{31}P$ NMR spectra.

## ASSOCIATED CONTENT

### Supporting Information

Additional experimental data are given in the Supporting Information file.

### Acknowledgments

Dedicated to Prof. Dr. Jan Michalski on the occasion of his 95th birthday.

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**Notes**

The authors declare no competing financial interest.

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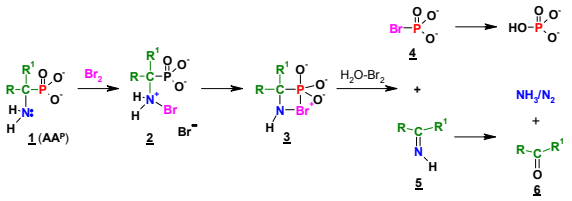
**Reactivity of Aminophosphonic Acids. Oxidative Dephosphonylation of 1-Aminoalkylphosphonic Acids by Aqueous Halogens**

Jozef Drabowicz, Frank Jordan, Marcin H. Kudzin, Zbigniew H. Kudzin, Christian V. Stevens and Pawel Urbaniak




The quantitative halogen-promoted dephosphonylation of $AA^P$ occurs via pentacoordinate phosphorus derivative **3** with formation of phosphoric acid, carbonyls and nitrogen.