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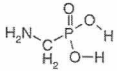
1-AMINOALKANEPHOSPHONIC ACIDS: SIX DECADES OF EXPLORATION

Abstract: 1-aminoalkanephosphonic acids (AA^P) are characterized in view of their syntheses, physicochemical properties and biological activity. The first part dealing with syntheses of AA^P is divided into seven sections describing the used synthetic methods; in the second part the UV and NMR spectroscopy results are presented along with chelating abilities of AA^P. The third part concerns the inhibition of enzymes by AA^P as well as antibacterial activity of these compounds.

1. Introduction

Chemistry of 1-aminoalkanephosphonic acids (aminophosphonic acids, AA^P) began with the lowest homologue synthesis of this class of compounds – aminomethanephosphonic acid (Gly^P), conducted by Engelmann and Pikl in 1942 [1,2].

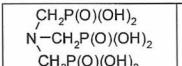
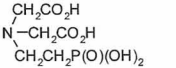
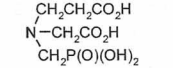
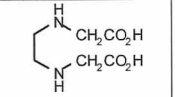
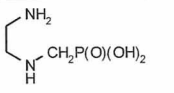
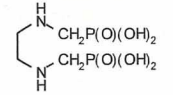
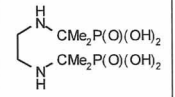
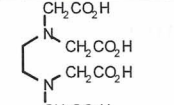
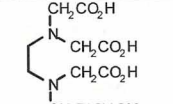
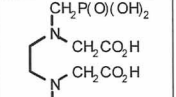
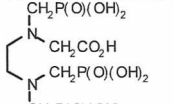
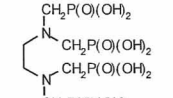
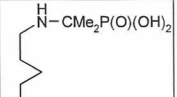
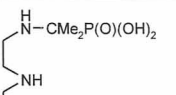
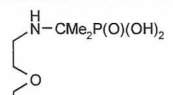
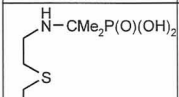
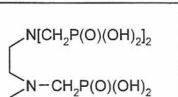
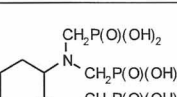


Gly^P

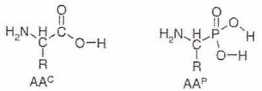
Because of the war-time, there was no desire for development of this – how it was judged then – cleanly academical investigative subject of matter. The research in the post-war period was undertaken, including investigations of physico-chemical properties of this new class of compounds as well as of their extension. Interesting chelating properties of the first phosphonic complexone-phosphonomethylene-aminodioacetic acid (NMPDA), synthesized by Schwarzenbach in 1949 [7], and also EDTMP – the phosphonic analogue of EDTA (EDTMP) obtained by Westerback and Martell [14] became the stimulus of further synthetic investigations (Table 1).

Table 1. Representative complexones and their aminophosphonate analogues [26]

Structure / Symbol	Structure / Symbol	Structure / Symbol
$N(CH_2CO_2H)_3$	$N(CH_2CO_2H)_2(CH_2P(O)(OH)_2)$	$N(CH_2CO_2H)(CH_2P(O)(OH)_2)_2$
NTA	NMPDA	NDMPA

 NTMP	 NEPDA	 NMPAPr
 EDDA	 EDMP	 EDDMP
 EDDIPP	 EDTA	 EDMPTA
 EDDMPDA	 EDTMPA	 EDTMP
 PDADIP	 DETADIP	 OPDADIP
 SPDADIP	 DETAPTMP	 CHDATP

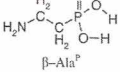
The structural analogy of natural carboxylic amino acids (AA^C) and the phosphonic amino acids (AA^P) suggested potential biological activity of AA^P.



AA^C AA^P

These suggestions found experimental confirmation very soon. In 1959 Horiguchi and Kandatsu isolated from a biological material the first aminophosphonic acid, namely 2- amino-ethanephosphonic acid (β-Ala^P) [16].

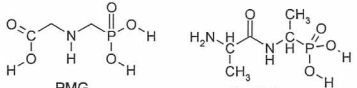
The works following this discovery witnessed a proliferation of papers demonstrating the occurrence of β-Ala^P, and other aminophosphonic acids in a wide range of living organisms (bacterias, protozoas) [136, 149, 274].



β-Ala^P

The subsequent biochemical experiments have shown that AA^P are able to form stable Schiff's bases with pyridoxal, and under physiological conditions undergo transamination [33, 222, 265, 273]. The structural analogy of aminophosphonic acids to carboxylic implied in consequence the mimetic behavior of AA^P expressed by inhibition of several enzymatic reactions, characteristic for natural amino acids [149].

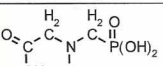
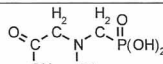
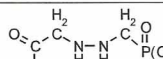
Therefore, biochemical properties of AA^P became stimulus for research programs relating to the metabolism of phosphonic compounds, especially these of the P-C-N class [186, 188]. It resulted in two equally spectacular events: the discovery of a strong antibacterial activity of mixed phosphonopeptides (in these Ala-Ala^P) and also in discoveries of antiherbicidal aminophosphonates, (in this a unique herbicide–phosphonomethyleneglycine; PMG).



PMG Ala-Ala^P

These discoveries caused a rapid development both in the field of synthesis of different phosphonopeptides [148, 279] and aminophosphonic herbicides [222, 265, 273]. In effect, number of described phosphonopeptides exceeds 200; representative aminophosphonic herbicides are listed in Table 2.

Table 2. Representative aminophosphonic herbicides [147, 186]

Structure / Symbol	Structure / Symbol	Structure / Symbol
 PMG	 APMG	 HPMG

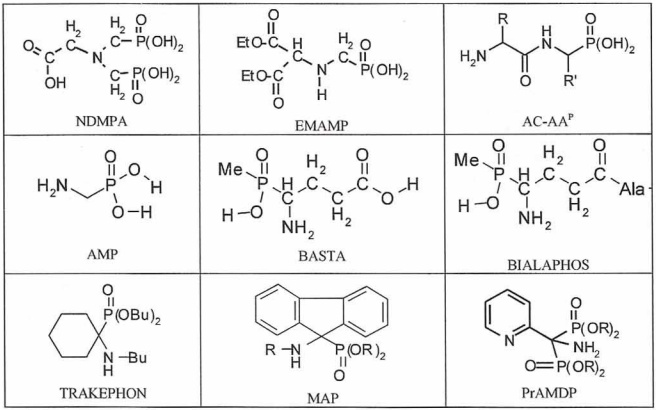
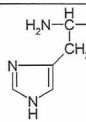
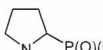
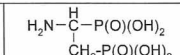
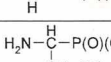
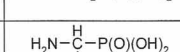
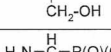
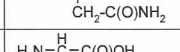
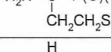
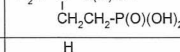
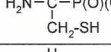
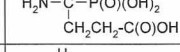
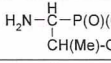
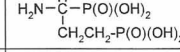
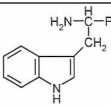
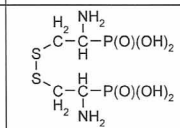


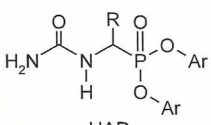
Table 3. Phosphonic analogues of protein amino acids

Aminophosphonic acids (AA^P)		Ref.[a]	Aminophosphonic acids (AA^P)		Ref.[a]
AA^P	Structure		AA^P	Structure	
Gly^P	$H_2N-C(H_2)-P(O)(OH)_2$	5,143, 168	His^P		192
Ala^P	$H_2N-C(H)(Me)-P(O)(OH)_2$	12,80,90			
Val^P	$H_2N-C(H)(CHMe_2)-P(O)(OH)_2$	19,80,90	Lys^P		146,237
Leu^P	$H_2N-C(H)(CH_2CHMe_2)-P(O)(OH)_2$	24, 80,90	Arg^P		41
Ile^P	$H_2N-C(H)(CH(Me)Et)-P(O)(OH)_2$	23,79,89	$Asp^{\beta\text{-}P}$		19
Phe^P	$H_2N-C(H)(CH_2Ph)-P(O)(OH)_2$	12, 80,90	$Asp^{\alpha\text{-}P}$		68

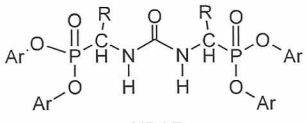
Pro^{P}		108,113	$Asp^{P,P}$		137,244
Ser^{P}		98,126, 150	Asn^{P}		68
Met^{P}		112	$Glu^{\alpha\text{-}P}$		15,18
Cys^{P}		125,139	$Glu^{\alpha,P}$		131
Thr^{P}		146	$Glu^{P,P}$		128.241
Tyr^{P}		191	Gln^{P}		
Trp^{P}		120,135	$[Cys^{P}]_2$		119

[a] The first and the most representative work

These events did not stay without influence on growing expectations concerning development of synthetic methods of this class of phosphonic compounds [53, 67, 179, 184, 185]. The breakthrough in this field can be connected with the work of Birum [50], which concerns an easy method of synthesis of phosphonic compounds of the C-P-N class, namely ureidoalkanephosphonates (UAP) and urylenebisalkanephosphonates (UBAP).



UAP



UBAP

The undertaking of the works over modification of the Birum reaction and its utilization as a preliminary stage in the synthesis of 1-aminoalkanephosphonic acids, afforded in effect a new class of synthetic methods of AA^P, characterized by unattainable up to here usable parameters, in this the tioureidoalkanephosphonate method [90, 265] and the amidoalkylation method [166, 181].

As a result of subsequent development of synthetic methods of AA^P, the list of phosphonic analogues of protein amino acids was quickly fulfilled (Table 3), accelerating in turn investigations on biochemical and biological activity of AA^P [273].

A rapid growth of interest in the class of the P-C-N compounds (especially in the recent decades) is reflected by the number over 5000 published works and patents relating to the aminoalkanephosphonates [181] as well as a number of general review papers [22, 26, 55, 67, 136, 177, 184, 265, 273]. Several papers reported on the methods of synthesis of AA^P [142, 185, 265, 275–278], their optical activity [173, 178], physical properties [281, 284], analysis [38, 97, 280, 284, 295, 297] and structural investigations [283], complexing abilities [26, 60, 97, 145], biological activity [101, 149, 158, 187, 286–291] and industrial application properties [26, 28, 265, 294].

2. Synthesis of 1-aminoalkanephosphonic acids

This chapter concerns the major types of the method of synthesis of 1-aminoalkanephosphonic acids, namely:

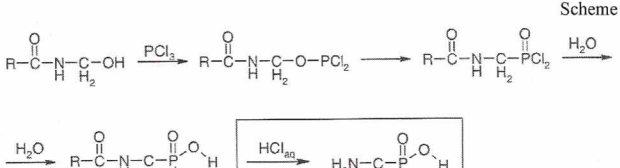
1. Methods based on simultaneous formation of P-C-N systems [P+C+N → P–C– N].
2. Methods based on nucleophilic substitution with phosphoroorganic nucleophiles [P + X–C–N → P–C–N + X].
3. Methods based on additions of the P-H functions to multiple bonds [P–H → P–C–N].
4. Methods based on α–amination of phosphonates and functionalized alkanephosphonates [P–C + N → P–C–N].
5. Methods based on modifications of the side chain of aminoalkanephosphonates [P–C(R)–N → P–C(R*)–N].
6. Methods based on modifications of phosphorus functions [P–C–N → P*–C–N].
7. Methods based on modifications of nitrogen functions [P-C-N → P-C-N*].

2.1. Methods based on simultaneous formation of P-C-N systems [P + C + N → P–C–N]

2.1.1. Reaction of amidoalkylation

The reaction of amidoalkylation of phosphorus trichloride worked out by Engelmann and Pikl in 1942 [1, 2], states chronologically the first method of synthesis of aminoalkanephosphonic acids. Authors' reaction proceeds according to the following scheme:

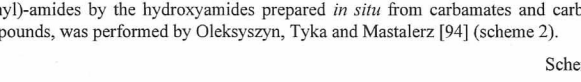
Scheme 1



The subsequent hydrolysis of intermediate N-acylaminomethylphosphonic acids [(AC)-Gly^P] led to phosphonoglycine (Gly^P) [5].

First essential modification of this method by replacement of starting N-(hydroxymethyl)-amides by the hydroxyamides prepared *in situ* from carbamates and carbonyl compounds, was performed by Oleksyszyn, Tyka and Mastalerz [94] (scheme 2).

Scheme 2

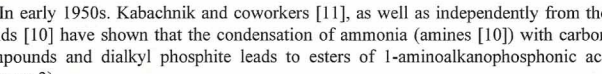


In subsequent extensions of this method, different amides including N-alkylcarbamates, and various trivalent phosphorus chlorides [93,130] as well as phosphorous acid [166] were used as substrates. These create the possibilities of synthesis of structurally diverse amino acids, in these – amino acids with phosphonic, phosphinic and phosphine oxide functions. Further investigations on application and mechanistic course of this reaction were continued by Soroka [181, 218, 219].

2.1.2. Reaction of Kabachnik-Fields

In early 1950s. Kabachnik and coworkers [11], as well as independently from them Fields [10] have shown that the condensation of ammonia (amines [10]) with carbonyl compounds and dialkyl phosphite leads to esters of 1-aminoalkanophosphonic acids (scheme 3).

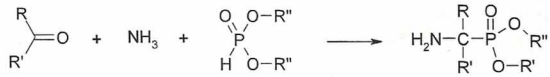
Scheme 3



As a result of condensation of amines with carbonyl compounds and dialkyl phosphite the esters of 1–[N–alkyl (aryl)]–, 1–[N,N–dialkyl (diaryl)]– or 1–[N,N–alkylarylamino]alkanephosphonic acids are formed [176, 293, 296, 301, 304].

The method of Kabachnik was the first general method of synthesis of 1-aminoalkanephosphonic acids bearing the primary amine group (scheme 4).

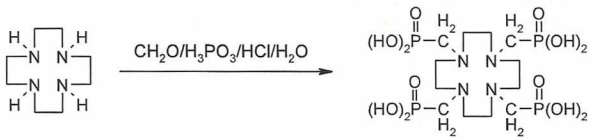
Scheme 4



The investigation of the mechanism of Kabachnik–Fields reaction was performed by Gancarz [236, 251, 267].

Many derivatives of Gly^P were prepared by the procedure of Modritzer and Irani, in which phosphorous acid reacted with amine and formaldehyde in strongly acidic solutions [20, 96]. Modern practical applications of this reaction are illustrated by the synthesis of phosphonylated azo-crown ethers [207, 253] (e.g. scheme 5).

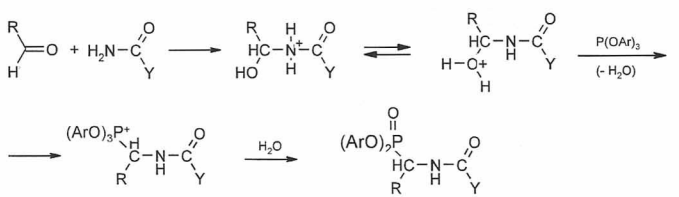
Scheme 5



2.1.3. Condensations of Birum type

The reaction of a similar category of transformations, being the variant of Arbuzov's reaction, was discovered by Birum in 1976 [50]. In this reaction, electrophilic reagents were prepared *in situ* from amide substrates and aldehydes, followed by addition of corresponding phosphites (scheme 6).

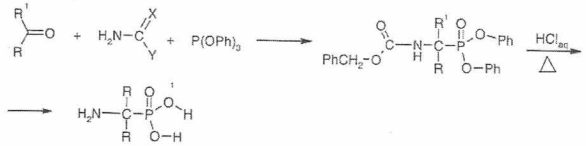
Scheme 6



Y = NH_2, R-NH, R_2NH; R = alkyl, aryl

The modifications of Birum reaction by application of easily degradable amide substrates, created a new type of convenient and high yield synthetic methods of AA^P (scheme 7) [185, 265, 275].

Scheme 7



X = O; Y = $PhCH_2OC(O)$-O; R, R' = alkyl, H; aryl, H; aralkyl, H; alkyl, alkyl
X = S; Y = Ph-NH-C(S)-NH-; R, R' = alkyl, H; aryl, H; aralkyl, H

As amide substrates – N-phenylurea [77, 103], benzyl carbamate (the carbamate-phosphonate method) [80, 107, 166] as well as thioureas (the thioureidoalkanephosphonate method) [90, 112, 119, 133, 139, 201, 213, 265] were used.

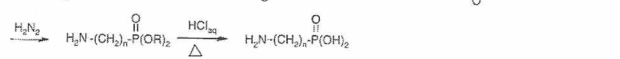
2.2. Methods based on nucleophilic substitution with phosphoroorganic nucleophiles [P + X–C–N → P–C–N + X]

2.2.1. Arbuzov and Michaelis-Becker reactions

One of chronologically early methods of synthesis of AA^P, worked out by Chavane and Hackspill, applied two classic reactions: Gabriel's and Michaelis-Becker's reactions [5, 12] (scheme 8).

Arbuzov and Michaelis-Becker reactions were used in the syntheses of derivatives of β-, γ-, and ω-aminophosphonic acids [4, 5, 40, 265], and also several rare AA^P, phosphonic derivatives of β-fluoroalanine [154] or ß-chloroalanines [162], containing different number of halogen atoms.

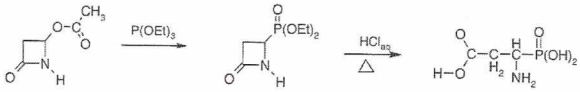
Scheme 8



n = 1-4; R = Et, Bu

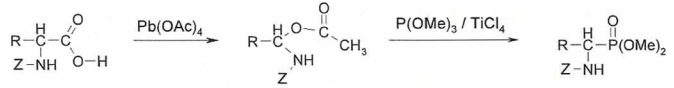
The synthesis of a phosphonic analogue of aspartic acid ($Asp^{\alpha P}$), starting from 4-acetoxyazetidin-2-ones [51, 130] is another example of application of Arbuzov reaction (scheme 9).

Scheme 9



In a similar manner the 1-aminoalkanephosphonates were obtained from carboxylic amino acids (AA^C), as a result of their conversion *via* semiaminal derivatives, and subsequent Arbuzov reaction [179, 210] (scheme 10).

Scheme 10

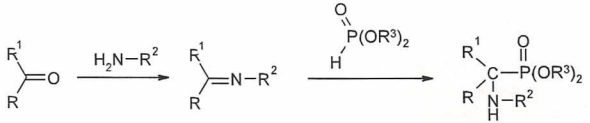


2.3. Methods based on addition of the P-H function to multiple bonds

2.3.1. Addition to multiple bonds: C=N, C=N–X, C≡N [P–H + C=N → P–C–NH]

The nucleophilic addition of phosphoroorganic reagents (usually bearing the P-H function) to C=N bonds is an important general method of synthesis of phosphonic compounds containing the P–C–N bond system, characteristic for 1-aminoalkanephosphonates [55,67,109,177,274,298, 303,304] (scheme 11).

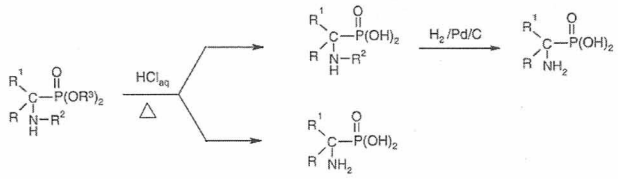
Scheme 11



Although the addition of phosphites to imines can occur without catalysts, the reaction is usually promoted by a base-acid catalysis [109, 275]. In majority, sodium ethoxide and triethylamine were applied for this purpose (basic catalysis), and also acids (e.g. HCl_g), among these Lewis acids (e.g. $ZnCl_2$ or $MgBr_2$) [275, 124].

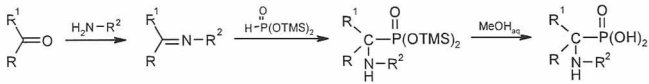
Application of benzylimines afforded corresponding 1-(N-benzylamino)alkanephosphonates, in which subsequent hydrolytic and/or hydrogenolytic deblockage of the amine group led to suitable aminophosphonic acids [31, 131] (scheme 12).

Scheme 12



The utilization of imines containing acid-labile N–X bonds, in this N-t-butyl [42], α,α-di-substituted benzylic groups [79], N-(1-phenylocyclopentyl) [91, 92], N-benzhydryl [116, 137] or N-trityl [195] groups, allowed elimination of the hydrogenolytic deblocking stage.

Scheme 13

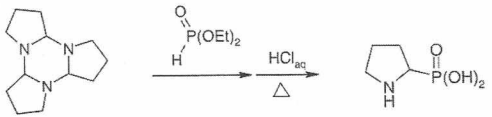


Different modifications depended on the applications of various trimethylsilyl and/or mixed trimethylsilyl-alkyl phosphites (scheme 13) [208, 265].

In the variant using imines of optically active α-phenylethylamine, a number of optically active 1-aminoalkanephosphonates were obtained [39, 76, 173]. The method of addition to the C=N bond was used to synthesize various aminophosphonic acids exhibiting potential bioactivity, in these the phosphonic analogues of morphactines [71, 262], proline [108, 131], penicillamine [153], lysine [197] or phosphinothiaproline [258].

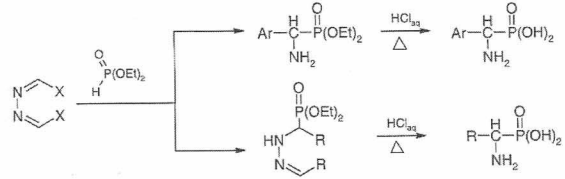
Hexahydrotriazines react like imines, affording in reaction with dialkyl- or diarylphosphites corresponding 1-aminoalkanephosphonates [47, 144, 265] (scheme 14).

Scheme 14



1-Aminoalkanephosphonic acids were also obtained by addition of diethyl phosphite to aromatic aldazines [48, 227] and aliphatic aldazines [64, 66], and also to aliphatic ketazines [95] (scheme 15).

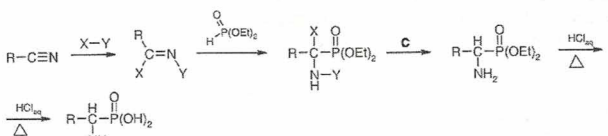
Scheme 15



X = alkyl (R), aryl (Ar)

AA^P may also be synthesized from imines generated *in situ* from nitriles (scheme 16) [75, 200].

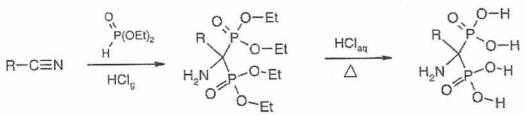
Scheme 16



R = alkyl, aryl; X-Y = i-Bu_2AlH, MeSH, H_2SnCl_4; **c**: reduction or solvolysis

The addition of dialkyl phosphites to nitriles affords esters of 1-aminoalkane-1,1-diphosphonates, subsequent hydrolytic deesterification of which leads to corresponding 1-amino-alkane-1,1-diphosphonic acids [109, 242] (scheme 17), compounds of a great pharmacological importance [234].

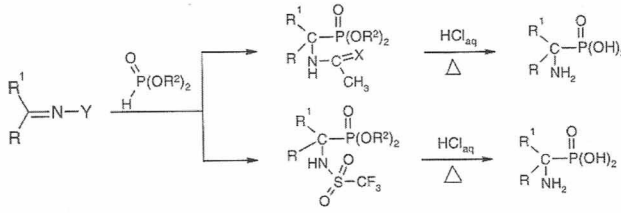
Scheme 17



R = alkyl, aryl

Also other types of the C=N substrates were used, including N-fluorosulphonyl-aldimines [25], N-acylimines [27, 265], N-acylthioimines [88, 89], nitrones [209, 265] and N-alkoxy-iminium salts [239], as well as N-sulphinoimines [268] (scheme 18).

Scheme 18

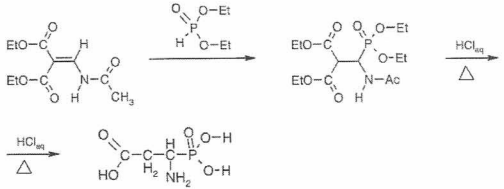


R, R^1 = H, alkyl, aryl; , R^2 = alkyl; X = O, S; Y = Me-C(X), CF_3-S(O)$_2$

2.3.2. Addition to multiple bonds C=C [P–H + C=C–N → P–C(C)–NH]

A phosphonic analogue of aspartic acid ($Asp^{\alpha P}$) was obtained in the addition of diethyl phosphite to acetamidomethylenemalonates [57, 68] (scheme 19).

Scheme 19



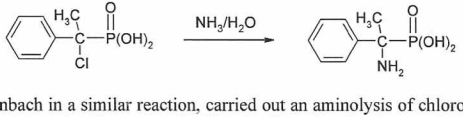
Asp^P

2.4. Methods based on α–amination of phosphonates and functionalized alkanephosphonates [P–C + N → P–C–N]

2.4.1. Nucleophilic amination

As early as in 1947 Kosolapoff conducted an ammonolysis of 1-chloro-1-phenylethanephosphonic acid, leading to corresponding amino acid with 12% yield [4].

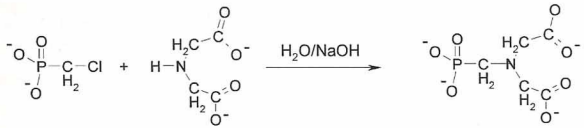
Scheme 20



Schwarzenbach in a similar reaction, carried out an aminolysis of chloromethylphosphonic acid using aminodiacetate, affording the first phosphonic complexone, namely, phosphonomethyleneamino-N,N-diacetic acid (NMPDA) [7] (scheme 21).

The reaction of ammonolysis of chloromethylphosphonic acid and its esters was studied by Kabachnik and Miedvied [8] and for chloromethylphosphinic analogues by Maier [106]. The reactions of ammonolysis and aminolysis of various halogenoalkanephosphonates (also phosphonites and aminophosphine oxides) were the object of several reviews [26, 53, 55].

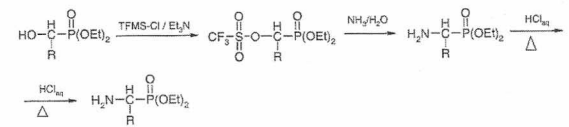
Scheme 21



In another approach, 1-hydroxyalkanephosphonates (HA^P) instead of 1-halogenoalkanephosphonates were applied. HA^P do not afford amine derivatives in a simple way by a direct nucleophilic substitution of the hydroxyl by amine function.

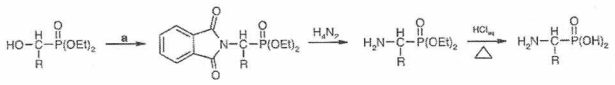
Therefore, the conversion of hydroxyl to the O-trifluoromethylsulphonyl function facilitating the nucleophilic substitution of this function, in this also the ammonolysis, (or aminolysis) is necessary [167] (scheme 22).

Scheme 22



As a result of activation of a hydroxyl function in the reaction of Mitsunobu, the starting 1-hydroxyalkanephosphonates were easily transformed into corresponding N-phthalimido-alkanephosphonates [127], hydrazinolysis and/or hydrolysis of which led to corresponding aminoesters and/or amino acids (scheme 23).

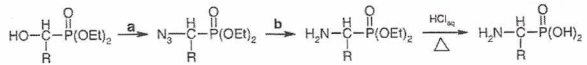
Scheme 23



a: Mitsunobu reaction

In a similar way 1-azidoalkanephosphonates were prepared, which in turn were reduced to iminophosphates or to aminoesters, and subsequently hydrolyzed to AA^P [229, 235] (scheme 24).

Scheme 24

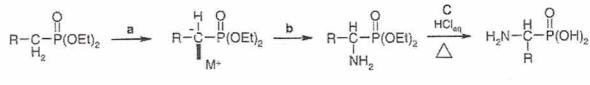


a: NaN_3 / azodicarboxylate; **b**: Ph_3P

2.4.2. Electrophilic amination

Alkanephosphonates containing acidic α–hydrogen atoms were transformed into α-carbanions, which in turn were submitted to electrophilic amination by O-(mesitylsulphonyl)hydroxylamine [82], O-(diphenylophosphinyl)hydroxylamine [129] or chloramine [194], or to hydrazination by azodicarboxylate reagent [241,249] (scheme 25).

Scheme 25



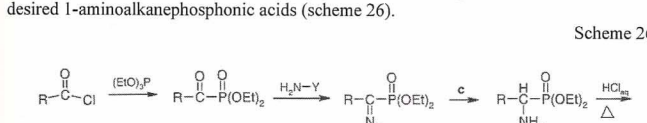
a: base; **b**: electrophilic amination; **c**: hydrolytic degradation

Thus, ethyl phosphonoacetate was converted *via* the α-carbanion stage to the corresponding oxime- or diazo-derivatives, reduced subsequently to a desired aminophosphonoacetate [194].

2.4.3. Reductive amination

This group of methods is based on transformation of 1-ketophosphonates. They were converted into hydrazones [6, 111, 265], oximes [23, 24, 118, 263] or imines [100–102], subsequent reduction of which afforded corresponding aminoester derivatives [265]. Moreover, acidolysis of intermediate diesters led to deblockage of the acidic function of desired 1-aminoalkanephosphonic acids (scheme 26).

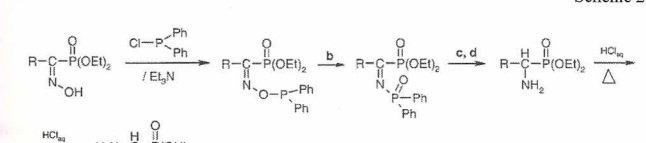
Scheme 26



R = alkyl, aryl, aralkyl; Y = H, HO, NH_2, NHPh, NMe_2; **c**: reduction

The conversion of 1-hydroxyiminealkanephosphonates into corresponding aminoesters, using O–phosphinylation of the hydroxyimine function (HO-N=), and spontaneous rearrangement of the O-phosphinyloxime to phosphinoamide function [P-O-N → P(O)-N], easily removable by acidolysis were also performed [191] (scheme 27).

Scheme 27



b: rearrangement; **c**: reduction; **d**: selective N- deblockage

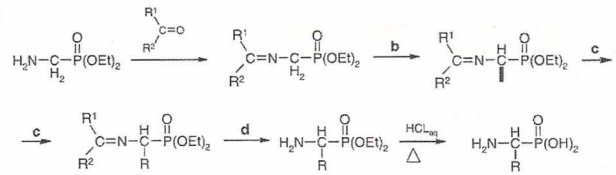
2.5. Methods based on modifications of the carbon skeleton of aminoalkanephosphonates [P-C-N → P-C(R)-N]

2.5.1. C_α-alkylation of phosphonoglycine derivatives

Conversion of aminomethanephosphonic acid esters [$Gly^P(OR)_2$] into suitable Schiff's bases [$R_2C{=}Gly^P(OR)_2$], followed by generation of carbanion (C_α) and nucleophilic alkylation, affords higher homologues [$R_2C{=}AA^P(OR)_2$]. Subsequent mild hydrolysis of these compounds yields corresponding intermediary O,O-dialkyl 1-aminoalkanephosphonates [$AA^P(OR)_2$]. The hydrolysis carried out under more drastic condi-

tions led finally to desired 1-aminoalkanephosphonic acids [AA^P] [74, 85, 188, 230, 231, 265] (scheme 28).

Scheme 28

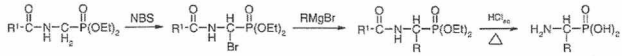


a: blocking of the amine function of $Gly^P(OEt)_2$; **b**: carbanion generation;
c: carbanion alkylation; **d**: deblockage of the amine function of $R_2C{=}AA^P(OEt)_2$;
e: hydrolytic deblockage of the acidic function of $AA^P(OEt)_2$ and AA^P isolation

Isonitrylomethanephosphonates undergo a similar reaction [121, 206].

In a different approach N-acylaminomethanephosphonates were converted into α-bromo derivatives, which were subjected to electrophilic alkylation by means of organo--magnesium [169] or organo-cupric [204] reagents. Formed 1-(N-acylamine)alkanephosphonates were subsequently hydrolyzed to free amino acids (scheme 29).

Scheme 29

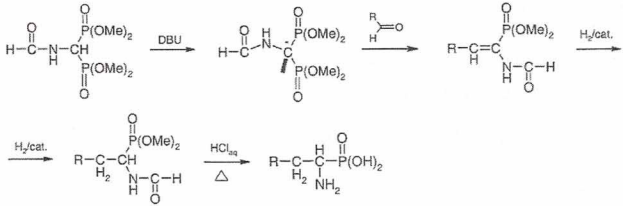


R^1 = alkyl, R = alkyl, aryl, aralkyl

2.5.2. Reactions of Horner-Wittig type

These reactions were applied by Schollkopf for synthesis of a number of optically active 1-aminoalkanephosphonic acids [161] (scheme 30).

Scheme 30

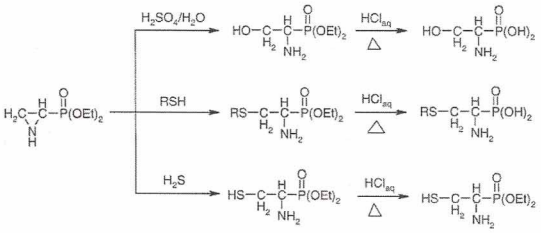


Similar reaction sequence was used by Tishler in the synthesis of histidine (His^P) [228].

2.5.3. Modifications of side chains of aminoalkanephosphonates

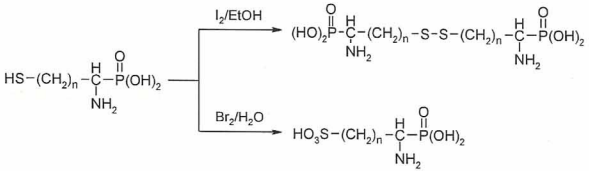
The transformations of aziridinealkanephosphonates [97, 119, 127, 163] (scheme 31) as well as α-(N-ethoxycarbonylimino)-α-(ethylthio)methylphosphonates [69] were performed.

Scheme 31



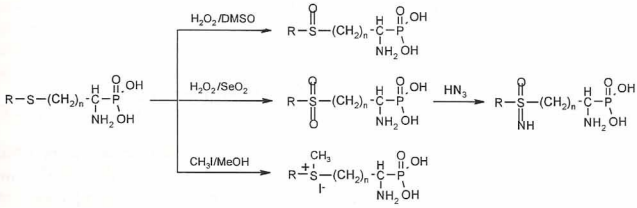
Oxidation of phosphonic analogues of thiolic acids - Cys^P and/or $Hcys^P$ affords, depending on the applied conditions, disulphide derivatives $[Cys^P]_2$ [119] and $[Hcys^P]_2$ [112] or sulphonic derivatives $Cys^P(A)$ or $Hcys^P(A)$ [307] (scheme 32).

Scheme 32



In a number of works the modifications of the thioether function of 1–aminothioalkanephosphonic acids were conducted, yielding corresponding sulphinyl and/or sulphonyl [133, 201, 244] as well as trimethylosulphonium derivatives [133] (scheme 33).

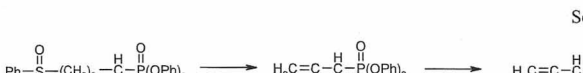
Scheme 33



1-Amine-3-sulphinyloalkanephosphonic acids were converted into sulphoxyiminium derivatives [203] (scheme 33).

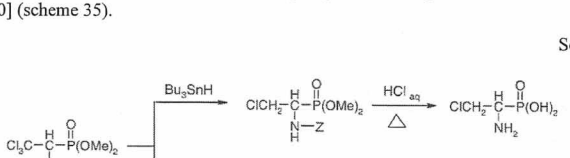
1-(N-acylamino)alkanephosphonates containing the sulphinyl function underwent thermal decomposition with conversion to 1-amine-2-propylenephosphonic acid [171] (scheme 34).

Scheme 34



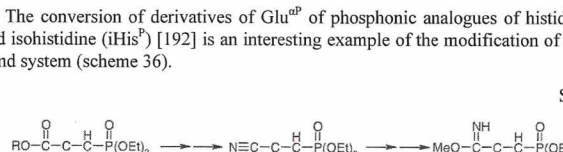
A selective reduction of the trichloromethyl function of 1-(N-acyloamino)-alkanephosphonates was used for synthesis of phosphonic analogues of chloroalanines [162, 170] (scheme 35).

Scheme 35



The conversion of derivatives of $Glu^{\alpha P}$ of phosphonic analogues of histidine (His^{P}) and isohistidine ($iHis^{P}$) [192] is an interesting example of the modification of the P-C-N bond system (scheme 36).

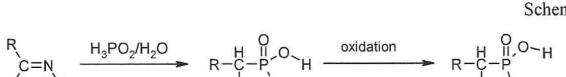
Scheme 36



2.6. Methods based on modification of phosphorus functions [P–C–N → P*–C–N]

Addition of hypophosphorous acid to imines (Y = H) [146], or oximes (Y = OH) [212] affords corresponding 1-aminoalkanephosphinic acids (AA^{PH}). AA^{PH} were oxidized to phosphonic analogues using the aqueous bromine reagent [146] or sulphuryl chloride [212] (scheme 37).

Scheme 37



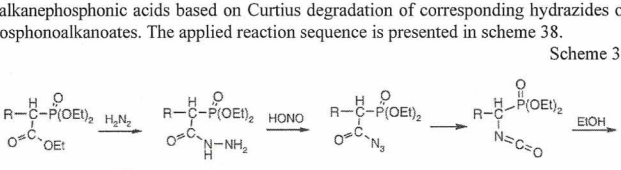
R = alkyl, aryl, aralkyl; Y = Ph_2CH, OH; Oxidants: Br_2/H_2O or SO_2Cl_2/H_2O

2.7. Modifications of functions containing nitrogen [P-C-N → P-C-N*]

2.7.1. Degradations of azide and amide functions

In 1964 Chambers and Isbell [19, 37] reported a new method of preparation of 1- aminoalkanephosphonic acids based on Curtius degradation of corresponding hydrazides of phosphonoalkanoates. The applied reaction sequence is presented in scheme 38.

Scheme 38



This method was used in the synthesis of a number of AA^P, including the synthesis of phosphonic analogue of tryptophan [135].

A related method of synthesis of AA^P involved Hoffmann's degradation of corresponding C-amides of aminocarboxylophosphonic acids. This method was also used in synthesis of both 1-aminoalkanephosphonic (α-AA^P) [49, 56], and 2–aminoalkanephosphonic (β-AA^P) [3, 30, 32] acids.

2.7.2. Reduction of functionalized alkanephosphonates bearing nitrogen containing groups

This reaction concerns discussed earlier [**2.4.3.**] methods of reduction of nitrogen derivatives of 1-ketophosphonates, such as hydrazones, oximes and imines. Aminophosphonic acids and aminophosphonic esters were also obtained by reduction of 1-azidoalkane-, 1-azoalkane- [194], 1-hydrazinoalkane- [66, 261] [**2.4.1**], and also 1-hydroxyloaminoalkanephosphonates [174].

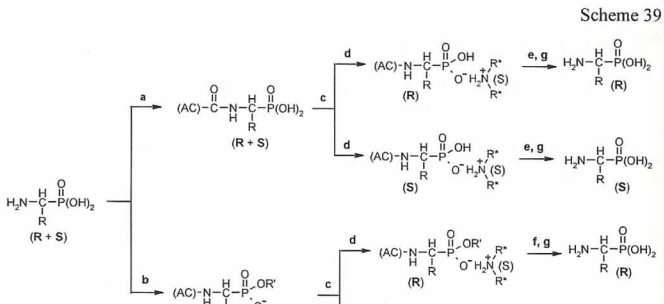
2.8. Synthesis of optically active 1-aminoalkanephosphonic acids

2.8.1. Resolution of diastereoisomeric aminoalkanephosphonates [141, 173, 178, 265, 278]

Aminophosphonic acids AA^P and their derivatives [N-acylamino acids – (AC)-AA^P, monoesters – $AA^P(OR)$, and diesters $AA^P(OR)_2$] were converted into diastereoisomeric

aminoalkanephosphonates. These compounds were separated into individual diastereoisomers (crystallization, liquid chromatography), which were subjected to deblockage of their aminoacidic functions. The main strategies applied for the resolution of racemic AA^P are presented in schemes 39–41.

Scheme 39



a: N-acylation of AA^P [$AA^P \rightarrow$(AC)-AA^P]; **b**: N-acylation and monoesterification of AA^P [$AA^P \rightarrow$ (AC)-AA^P(OR')]; **c**: reaction of (AC)-AA^P [or (AC)-AA^P(OR')] with optically active amines (e.g. with S configuration); **d**: resolution of diastereoisomeric pairs [(S, **S**) and (S, **R**)]; **e**: deacylation of (AC)-AA^P; **f**: deacylation and deestrification of (AC)-AA^P(OR'); **g**: isolation of enantiomeric AA^P.

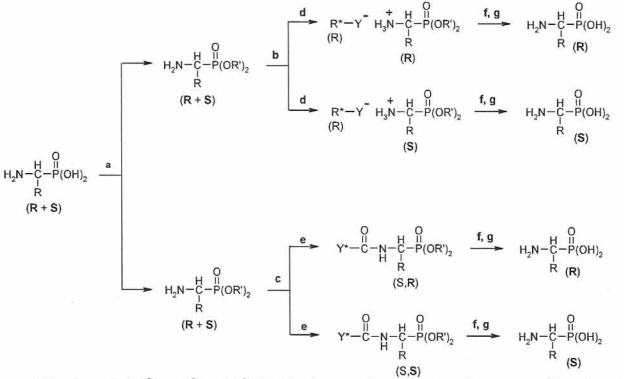
Thus, racemic $AA^P(OR)_2$ were converted into diastereoisomeric salts or amides by reaction with optically active acids, their anhydrides or chlorides (derivatives of tartaric and/or sulphocamphoric acids). The diastereoisomeric pairs formed, after subsequent separation, were converted to enantiomeric AA^P (scheme 40).

In another approach, l-(N-acylamino)alkanephosphonic acids [(AC)-AA^P] as well as their monoesters [(AC)-AA^P(OR)] were transformed into diastereoisomeric salts with optically active amines (α-phenylethylamine, ephedrine, quinine and/or dehydroabiethylamine), and after separation by crystallization, were converted to enantiomeric AA^P (scheme 40).

2.8.2. Enzymatic resolution of 1-(N-acylamino)alkanephosphonates

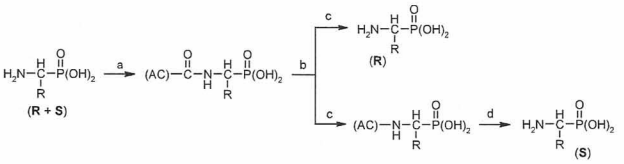
The racemic l-(N-acylamino)alkanephosphonates (R + S) were subjected to enzymatic hydrolysis catalyzed by acylases. These caused enantioselective splitting of the amide bond of enantiomers (R)-(AC)-AA^P, with simultaneous retention of enantiomers (S)-(AC)-AA^P [220,226,238,240,254,271]. Separation of mixtures of (R)-(AC)-AA^P and (S)-AA^P, and subsequent acidolysis of isolated (R)-(AC)-AA^P, afforded both enantiomeric acids, namely (R)-AA^P and (S)-AA^P (scheme 41).

Scheme 40



a: esterification of AA^P [$AA^P \rightarrow AA^P(OR)_2$]; **b**: reaction of aminodiesters $AA^P(OR)_2$ with optically active acids R*-YH (e.g. with R configuration); **c**: reaction of aminodiesters $AA^P(OR)_2$ with anhydrides or chlorides of optically active acids (e.g. with R configuration) [$AA^P(OR)_2 \rightarrow$ Y*-C(O)-$AA^P(OR)_2$]; **d**: resolution of diastereoisomeric salts [R*YH×$AA^P(OR)_2$: (S,**S**) and (S,**R**)]; **e**: resolution of diastereoisomeric amides [Y*-C(O)-$AA^P(OR)_2$: (R,**R**) and (R,**S**)]; **f**: deblockage of blocked amino-acidic functions; **g**: isolation of enantiomeric AA^P.

Scheme 41



a: N-acylation of AA^P; **b**: enzymatic deacylation of one enantiomeric N-acyloamino-alkanephosphonates [(R)-(AC)-AA^P]; **c**: separation of (R)-AA^P and (S)-(AC)-AA^P; **d**: deacylation of (S)-(AC)-AA^P and isolation of (S)-AA^P.

2.8.3. Asymmetric synthesis of 1-aminoalkanephosphonic acids

Many of presented above methods of aminophosphonic acids synthesis were adapted for their asymmetric synthesis, in particular;

— addition of dialkyl phosphites to chiral imines [39, 76, 250];
— addition of chiral phosphites to cyclic imines [155];
— asymmetric hydrogenation [161, 256, 259, 264];
— addition of phosphites to chiral glycosylonitrones [134, 156];

— oxidation of optically active 1-aminoalkanephosphinic acids [146, 252];
— alkylation of optically active derivatives of phosphonoglycinate [180, 190, 211, 224, 231, 232, 260];
— amination of optically active 1-hydroxyalkanephosphonic acids [229, 233].

This topic is a subject of several review works [177, 248, 265, 278].

3. Physicochemical properties of 1-aminoalkanephosphonic acids

3.1. General physical properties

Aminophosphonic acids are colourless crystalline substances characterized by their high melting points (melting *vs.* decomposition), comparable with those of corresponding carboxylic amino acids (Table 4).

Table 4. Melting-point (decomposition) and the solubility in water of natural amino acids (AA^C) and their phosphonic analogues (AA^P)

AA^C	Melting temp. (decomp.)[199] [°C]	Solubility at 25 °C[199] [g/100 ml]	AA^P	Melting temp. (decomp.)[Literature] [°C]
Gly	292	25.	Gly^P	286.5[19]; >300[5]; 338-344[205]
Ala	290	16.6	Ala^P	275-276[90]; 283-285[19]
Val	315	8.9	Val^P	261-262[90]; 271[19]; 279-283[218]
Leu	337	2.4	Leu^P	279[24]; 293-294[146]
Ile	284	4.1	Ile^P	271-272[44]; 274[24]
Pro	222	16.2	Pro^P	266-267[113]; 275-278[108]
Phe	284	3.0	Phe^P	225-227[12]; 267-269[90]; 281[19]
Ser	228	5.0	Ser^P	80[98]; 95-110[196]; 186-188[15]; 210-212[156]
Thr	255	20.5	Thr^P	212-215[146]; 220-221[261]; 221-223[300]
Tyr	344	0.05	Tyr^P	258-260[216]
Met	283	3.5	Met^P	270-272[112]
Cys	220		Cys^P	228-234[127]; 251.5-252.5[139]
$[Cys]_2$	260	0.01	$[Cys^P]_2$	257-259[119]
Arg	238		Arg^P	
Lys	224		Lys^P	275-277[243]; >300[146]
His	277	0.43	His^P	255-256[192]
Trp	282	1.1	Trp^P	260-261[122]; 280-281[135]
Asp	270	0.5	$Asp^{\alpha\text{-}P}$	234-238[57]
			$Asp^{\beta\text{-}P}$	228[19]; 228-232[68]
			$Asp^{P,P}$	233-235[137,246]; 234-236[200]
Asn	236	3.0	$Asn^{\alpha\text{-}P}$	247-252[57]
Glu	249	0.96	$Glu^{\alpha\text{-}P}$	167-169[130]
			$Glu^{\beta\text{-}P}$	247-252[57]
			$Glu^{P,P}$	237-239[137]; 236-238[246]
Gln	186	3.6	Gln^P	

Aminophosphonic acids have a moderate solubility in water, lower than that of their carboxylic analogues [265]. The solubility of AA^P increases in basic solutions (pH > pH_i) and acidic solutions (pH < pH_i), i.e. in pH regions beyond their isoelectric points. Solubility of AA^P in neutral organic solvents is very low.

3.2. Spectroscopic properties of aminophosphonic acids

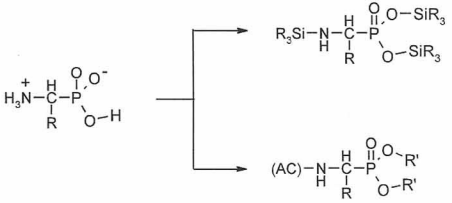
The spectroscopic, IR, ^1H NMR, ^{31}P NMR and ^{13}C NMR investigations of functionalized phosphonic acids as well as of AA^P, were the object of an intense multi-disciplinary research [255, 265, 281], including X-ray crystallographic studies [266, 283]. The dependence of the chemical shift of phosphorus nuclei of AA^P on pH, resulting in an obvious way from protonation degree of the functional groups of the amino acid, was reported in numerous works [106, 225, 244, 246].

Aminophosphonic acids were also characterized by mass spectrometry, FAB and CI methods [245, 265, 284].

3.3. Chromatographic properties of aminophosphonic acids

Chromatographic investigations of AA^P [54, 78, 104, 265, 280, 292] and their N–substituted derivatives (R-AA^P and R_2AA^P) [46, 265] were carried out by use of liquid chromatography. Analysis of these nonvolatile compounds (Table 4) by the method of gas chromatography requires their previous transformation into volatile derivatives, usually O,N-persilyl aminoalkanephosphonates or O,O-dialkyl 1-(N-acylamino)-alkane-phosphonates [284] (scheme 42).

Scheme 42



GC/MS/EI investigations were performed for persilyl-derivatives of AA^P and their aminoesters, esters of l-(N-acyloamino)alkanephosphonic acids, as well as bistrimethylsilyl esters of N-derivatives of AA^P [namely, Ac-$AA^P(OTMS)_2$, Me_2C=-$AA^P(OTMS)_2$ and SC=$AA^P(OTMS)_2$] [284].

3.4. Optical activity of 1–aminoalkanephosphonic acids [72, 141, 173, 265, 278]

Aminophosphonic acids, like their carboxylic analogues, possess asymmetric carbon atoms (except for Gly^P) and therefore they show optical activity. The comparison of optical rotations of both classes of amino acids (AA^C *vs* AA^P) is presented in Table 5.

Table 5. Comparison of optical rotations of AA^C and corresponding AA^P

AA^C	Optical rotations [199] $[M]_D$ and $([\alpha]_D)$		AA^P	Optical rotations [173] $[M]_D$ and $([\alpha]_D)$	
	H_2O[a]	5 M HCl $_{aq}$ [a]		R	S
Ala	1.6 (1.8)	13.0 (14.6)	Ala^P	-17.0 (1N NaOH)	17.0 (1N NaOH)
Val	6.6 (5.6)	33.1 ()	Val^P	+0.6 (1N NaOH)	-0.6 (1N NaOH)
Leu	-14.4 (-11.0)	21.0 (16.0)	Leu^P	-28.0 (1N NaOH)	27.0 (1N NaOH)
Ile	16.3 (12.4)	51.8 (39.5)	Ile^P	-8.5 (1N NaOH)/ [271]	
Pro	-99.2 (-86.2)	-69.5 (-60.4)	Pro^P	64.0 (1N NaOH)	-60.0 (1N NaOH)
Phe	-57.0 (-34.5)	-7.4 (-4.5)	Phe^P	-49.0 (1N NaOH)	52.0 (1N NaOH)
Ser	-7.9 (-7.5)	15.9 (15.1)	Ser^P	-30.0 (1N NaOH)	35.0 (1N NaOH)
Thr	-33.9 (-28.5)	-17.9 (-15.0)	Thr^P	-10.2 (H2O)/ [300]	
Tyr		-18.1 (-10.0)	Tyr^P	-53.0 (1M HCl)	
Met	-14.9 (-9.8)	34.6 (23.2)	Met^P	-40.4 (1N NaOH)	38.1 (1N NaOH)
Cys	-20.0 (-16.5)	7.9 (6.5)	Cys^P		
Arg	21.8 (12.5)	48.1 (27.6)	Arg^P		
Lys	19.7 (13.5)	37.9 (25.9)	Lys^P		
His	-59.8 (-38.5)	18.3 (11.8)	His^P		
Trp	-68.8 (-33.7)	-5.7 (-2.8)	Trp^P		
Asp	6.7 (5.0)	33.8 (25.4)	Asp^{I-}_P	-32.6 (H2O)	
Asn	-7.4 (5.6)	-7.4 (-5.6)	Asn^{I-}_P	-33.0 (H2O)	
Glu	17.7 (12.6)	46.8 (31.8)	$Glu^{I-}P$	-20.0 (1N NaOH)	21.0 (1N NaOH)
Gln	9.2 (6.3)	46.5 (31.8)	Gln		

[a] Data consider L-AA^C; c = 1-2 g AA / 100 mL; temp. 25 °C.

3.5. Protonolytic dissociation/protonation equilibria of 1-aminoalkanephosphonic acids

The equilibria of protonation and complexation of aminophosphonic acids are the object of several works [56, 73, 99, 103, 228]. Generally, AA^P show higher acidity both in comparison with carboxylic amino acids (AA^C), and with alkanephosphonic acids. The dissociation constants of natural amino acids (AA^C) and their phosphonic analogues (AA^P) are listed in Table 6.

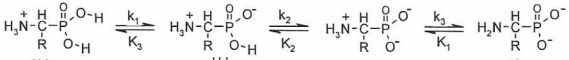
Table 6. Logarithms of dissociation constants of natural amino acids (AA^C) and their phosphonic analogues (AA^P)

AA^C	pK_i [199]			AA^P	pK_i Literature				
	pK_1	pK_2	pK_3		pK_1	pK_2	pK_3	pK_4	pK_5
Gly	2.34	9.60		Gly^P	0.38[110]	5.47[272]	10.16[272]		
Ala	2.34	9.60		Ala^P	0.38[110] 1[223]	5.76[272]; 5.55[223,243]	10.25[272]; 10.11[223,243]		
Val	2.32	9.62		Val^P	0.62[110] 1.23[146]	5.80[110] 5.68[146]	10.35[110] 10.46[146]		
Leu	2.36	9.60		Leu^P					
Ile	2.36	9.68		Ile^P					
Pro	1.99	10.6		Pro^P					
Phe	1.83	9.13		Phe^P		9.62[175]	5.43[175]		

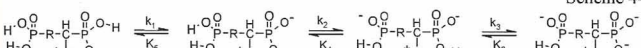
Ser	2.21	9.15		Ser^{P}					
Thr	2.71	9.62		Thr^{P}		5.30[243]	9.28[243]		
Tyr	2.20	9.11		Tyr^{P}					
Met	2.28	9.21		Met^{P}	<1[112]	5.65[112]	9.74[112]		
Cys	1.71	8.27	10.8	Cys^{P}	<1[139]	5.26[139]	8.90[139]	11.0[139]	
Arg	2.17	9.04	12.8	Arg^{P}					
Lys	2.18	9.12	10.5	Lys^{P}		5.76[243]	9.7[243]	11.1[243]	
His	1.82	6.00	9.17	His^{P}					
Trp	2.38	9.39		Trp^{P}					
Asp	1.88	3.65	9.60	$Asp^{\alpha\text{-}P}$					
				$Asp^{\beta\text{-}P}$	1.91[182]	6.15[272] 6.38[182]	10.1[272] 11.1[182]		
				$Asp^{P,P}$	<1[246]	1.06[246]	5.19[246]	6.55[246]	10.30[246]
Asn	2.02	8,80		$Asn^{\alpha\text{-}P}$		5.22[270]	9.05[270]		
Glu	2.16	4.32	9.96	$Glu^{\alpha\text{-}P}$		3.6[182]	5.2[182]	10.4[1182]	
				$Glu^{\gamma\text{-}P}$		6.85[272] 2.26[270]	10.7[272] 2.52[270]	6.81[270]	10.0[270]
				$Glu^{P,P}$	<1[246]	1.07[246]	5.56[246]	6.92[246]	10.43[246]
Gln	2.17	9.13		Gln^{P}					

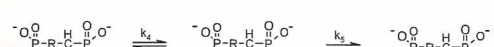
Dissociation/protonation equilibria for various AA^{P} are presented in schemes 43 (bifunctional AA^{P}: Gly^{P}, Ala^{P}, etc), 44 (diphosphonic AA^{P}: $Asp^{P,P}$, $Glu^{P,P}$) and 45 (phosphonic-diamino AA^{P}: Lys^{P}).

Scheme 43

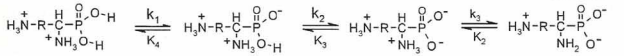


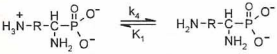
Scheme 44





Scheme 45





3.6. Chelating abilities of aminophosphonic acids [26, 43, 53, 60, 145, 210, 214, 217, 265, 269, 282]

Comparison of chelating abilities of aminophosphonic acids and amino acids is shown in Table 7, and comparison of stability constants of standard complexes of representative aminophosphonic and aminocarboxylic complexones is given in Table 8. Chelatic abilities of aminophosphonic acids are similar as those of their carboxylic analogues (cations of transition metals), with a general trend of their growth with an increase of the number of phosphonic functions in the molecule. Generally, AA^P contrary to AA^C, are able to form stable complexes in acidic solutions.

Table 7. Logarithms of stability constants of natural amino acids (AA^C) and their phosphonic analogues (AA^P) [282]

Metal	Ligand	$\log K_{MA}$	$\log K_{MA2}$	$\log K_{MA^*}$	$\log K_{MA2^*}$
Cu(II)	α-Ala	8.04	6.69	-3.99	-5.34
	α-Ala^P	8.29	6.65	-7.37	-9.01
	α-Ala^{Po}	4.87	4.04	-4.16	-4.99
	α-Ala^{Pi}	4.54	4.54	-3.84	-4.75
Ni(II)	α-Ala	5.32	4.42	-6.71	-7.61
	α-Ala^P	5.42	3.89	-10.24	-11.77
Co(II)	α-Ala	4.24	3.41	-7.79	-8.62
	α-Ala^P	4.55	3.15	-11.11	-12.51
Zn(II)	α-Ala	4.56	3.95	-7.67	-8.62
	α-Ala^P	5.99	-	-9.67	-
Cu(II)	β-Ala	6.91	5.45	-6.65	-8.11
	β-Ala^P	8.53	6.43	-8.60	-10.70
Ni(II)	β-Ala	4.52	3.32	-9.04	-10.24
	β-Ala^P	5.34	3.70	-11.79	-13.24
Co(II)	β-Ala	3.49	2.59	-10.07	-10.97
	β-Ala^P	5.16	3.66	-11.97	-13.42
Zn(II)	β-Ala	3.78	3.12	-8.78	-10.44
	β -Ala^P	6.09	4.85	-11.04	-12.28

$\log K_{MA^*} = \log K_{MA} - \sum pK$ – for reaction: $M^{2+} + H_nA = MA + nH^+$

$\log K_{MA2^*} = \log K_{MA2} - \sum pK$ – for reaction: $M^{2+} + H_nA = MA_2 + nH^+$

Table 8. Logarithms of stability constants of standard complexes of representative aminophosphonic and aminocarboxylic complexones [26]

Complexone (symbol)	K_i	log							
		Mg^{+2}	Ca^{+2}	Co^{+2}	Ni^{+2}	Cu^{+2}	Zn^{+2}	Fe^{+3}	La^{+3}
NTA	K_1	5.41	6.41	10.61	11.26	12.68	10.45	15.9	
AMPDA	K_1	1.96	6.28	2.43	7.18				
ADMPA	K_1		6.17	5.44	12.53		14.65		
AEPDA	K_1	2.14	6.33	2.05	5.44				
AMPPA	K_1		4.88	7.20	13.0		16.3		

EDTA	K_1	2.28	3.51	3.09	5.20	5.58	3.28		3.28
	K_2	8.69	10.59	16.31	18.62	18.80	16.50	25.1	15.50
EDDMP	K_1	-	-	3.84	4.71	8.72	5.02	>8	cryst.
	K_2	<2	<2	10.80	12.02	18.58	12.04	7.49	
EDDIP	K_1	-	-	3.84	3.84	8.63	4.81	>10	5.37
	K_2	<2	<2	11.19	11.23	20.35	13.38	>15	10.13

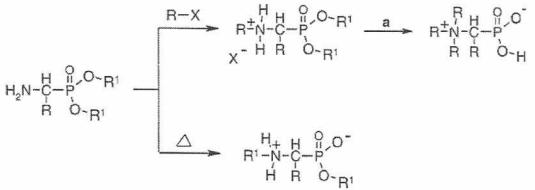
$K_1 = K_{MA}$; $K_2 = K_{MA2}$

3.7. Reactions of amino group

The consequence of discussed earlier (**3.5.**) protolytic equilibria of AA^P is their occurrence in acid solutions in the form of protonated salts (e.g. hydrochlorides), low stability of which makes their isolation difficult. Much more stable are salts of corresponding aminoesters $[AA^P(OR)_2]$, e.g. hydrochlorides, picrates, oxalates [177, 265]. Salts of aminoesters and optically active organic acids may be used for resolution of racemic AA^P (**2.1.8.1.**).

The amino group of aminoesters easily undergoes N-alkylation [9], which for O,O-dimethyl 1-aminoalkanephosphonates proceeds spontaneously as a result of the internal rearrangement [87, 265] (scheme 46).

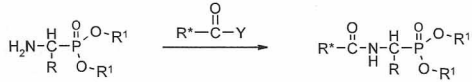
Scheme 46



a: exhaustive N-alkylation (R-X/base) and subsequent hydrolysis

The N-acylation of amino-esters with anhydrides or acyl chlorides (in presence of an appropriate base) [13, 265] affords corresponding N-acylaminoalkanephosphonates (scheme 47).

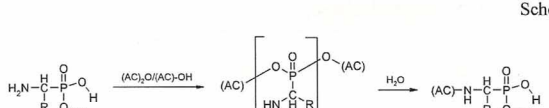
Scheme 47



Y = Cl or acyl moiety

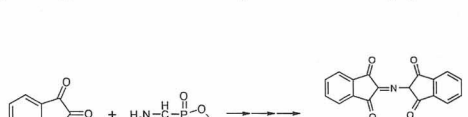
The reactions of N-acylation of free AA^P are more difficult, they proceed *via* mixed phosphono-carbonic anhydrides as intermediates [306] (scheme 48).

Scheme 48



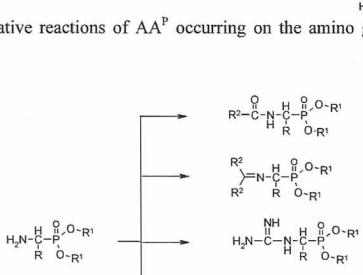
In reaction with ninhydrin AA^P show colours characteristic for amino acids [19, 21] (scheme 49), enabling detection of these compounds in chromatographic analysis [265].

Scheme 49



Some representative reactions of AA^P occurring on the amino group, are given in scheme 50.

Scheme 50



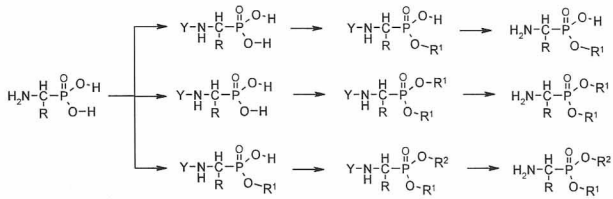
Thus, aminophosphonic acids [33, 96, 172, 262, 265] and their esters [74, 85, 131, 265] in reaction with aldehydes afford aldimines, and in reaction with cyanamide [35] or S-ethyl-isothiourea [81] are converted into corresponding guanidinealkanephosphonic acids. AA^P in reaction with nitrous acid form unstable diazo derivatives, decomposing at ambient temperature with emission of nitrogen [34, 59]. Oxygenation of AA^P leads to corresponding 1-nitroalkanephosphonic acids [65].

3.8. Reactivity of the phosphonic function

The reactions of a phosphonic group of AA^P, its conversion to monoesters [$AA^P \rightarrow AA^P(OR)$ and/or $AA^P \rightarrow$ (AC)-$AA^P(OR)$], diesters [$AA^P \rightarrow AA^P(OR)_2$ and/or $AA^P \rightarrow$

(AC)-$AA^P(OR)_2$], including formation of an asymmetrical diester function [$AA^P \rightarrow AA^P(OR)(OR')$ and/or $AA^P \rightarrow$ (AC)-$AA^P(OR)(OR')$], and also a selective and mild deblocking of phosphonic functions [$AA^P(OR)_2 \rightarrow AA^P$ and/or (AC)-$AA^P(OR)(OR') \rightarrow$ (AC)-$AA^P(OR) \rightarrow AA^P(OR)$], belong to problem-of-arts of the chemistry of mixed peptides (scheme 51).

Scheme 51



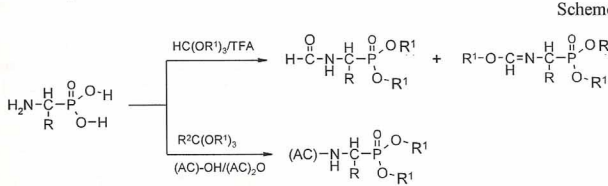
Y = H or acyl; R, R^1 or R^2 = alkyl, aralkyl or aryl

This group of reactions was discussed in detail in a monograph by Kafarski, Mastalerz and Lejczak [148]. The diesters are synthesized by esterification of N-acylaminoalkanephosphonic acids with diazoalkanes [52, 86, 115] or O-benzylisourea [189], and also by treatment of AA^P with orthoesters [265]. The monoesters [$AA^P(OR)$] were obtained in condensation of N-protected aminophosphonic acids (Y-AA^P) with suitable alcohols in the presence of pyridine and trichloroacetonitril [61,123], DCC [109] or thionyl chloride in DMF [265]. The monoesters are also formed in basic hydrolysis of corresponding O,O-dialkyl N-acyloaminoalkanephosphonates [(AC)-$AA^P(OR)_2$] [117, 265].

An exhausting esterification of monoesters leads to asymmetrical diesters [$AA^P \rightarrow AA^P(OR) \rightarrow AA^P(OR)(OR')$], characterized by different stability of both ester functions ($P\text{-}OR^1$). For introduction of the second ester function various reagents were used, among them diazoalkanes [67, 86, 123], alkylating reagents [95] or orthoformates [265] (scheme 51). Several selective conversions of monoesters into diesters were reported by Wasilewski et al. [70, 265].

Simultaneous N-acylation and P-O-estrifications of AA^P occurred in their reaction with orthoesters [265] or anhydrides/orthoesters mixtures [247, 257, 265, 299, 302, 305] (scheme 52).

Scheme 52

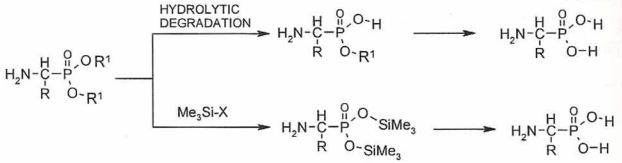


R^1 = Me, Et; R^2 = H, Me; (AC)- = $CH_3C(O)$-; $CF_3C(O)$-

AA^P undergo condensation with nucleosides and nucleotides to give monoesters [29, 105] or mixed anhydrides of the type AA^P-AMP [100, 101].

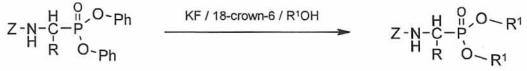
Hydrolysis of diesters, usually performed in acidic, and sometimes in basic solutions, leads mainly to free AA^P [265]. It was found that the deestrification under mild conditions requires the use of halogenosilanes [98, 122, 265] (scheme 53).

Scheme 53



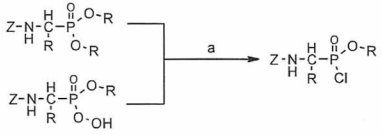
Aryl groups such as benzyl, phenyl or diphenylmethyl can be removed by hydrogenolysis [265]. O,O-Diphenyl 1-(benzoxycarbonylamino)alkanephosphonates can be easily converted into corresponding O,O-dialkyl derivatives by transesterification with potassium fluoride/crown ethers catalysts [132,220] (scheme 54).

Scheme 54



Diesters or monoesters of N–protected AA^P can be converted to the corresponding chloroesters by treatment with thionyl chloride [117] or phosphorus pentachloride [151, 265] (scheme 55).

Scheme 55



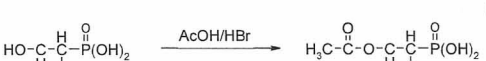
a: $SOCl_2$ or PCl_5

Reviews concerning derivatization of phosphonic functions of phosphonic and/or aminophosphonic acids (herbicides, chemical warfare or their metabolites and/or products of their degradations) were recently published by Stalikas et al. [295, 297] and by Black and Muir [302].

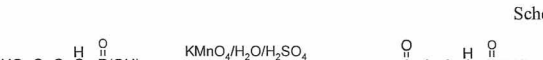
3.9. Reactions on the side chain

Reactions of this type include the O-acetylation of Ser^P [98] (scheme 56), the oxidation of $Hser^P$ [134] (scheme 57), and also reactions carried out on the phenyl ring of Phe^P [138], applied to assignment of absolute configuration of these amino acids.

Scheme 56



Scheme 57



4. Biochemical activity and biological properties of aminophosphonic acids [148, 149, 222, 273]

Aminophosphonic acids, being structural analogues of natural amino acids, exhibit antagonistic action against them (AA^P *vs.* AA^C) and compete with AA^C for active places of enzymes and/or cellular receptors.

AA^P acting as inhibitors of metabolic processes show physiological activity as antibacterial agents, neuroactive compounds [287], antithrombic agents [290] or inhibitors of human colagenase [291], anticancer drugs or pesticides, an area of possible applications of which expands from medicine to agricultural chemistry [222]. They also play an important role in a design of transition state analogue inhibitors [288] and/or in a design and synthesis of HIV protease inhibitors [289].

An important source of the biological activity of AA^C is their structural similarity to AA^P, along with substantial differences of phosphonic and carboxylic functions. These include the size (the phosphonic group is considerably larger), the spatial structure (a carboxyl is flat when the phosphonic is tetrahedral) and acidity (AA^P are two-protonic and also stronger acids than corresponding mono-protonic AA^C; for pK differences see Table 6).

The major areas of biochemical activity of AA^P are expressed by:

— inhibition of enzymes [222, 288–291];
— antibacterial activity [83, 99, 222];
— plant growth regulation activity [62, 186, 222, 286];
— neuromodulatory activity [222, 287].

The most relevant review papers on this topic were written by Kafarski, Lejczak and Mastalerz [142, 148, 222], and also edited by Hudson and Kukhar [273].

4.1. Inhibition of enzymes by AA^P [222]

The history of enzymes inhibition by AA^P begins in 1959, when Mastalerz reported on an inhibition of the glutamate synthetase by some phosphonic analogues of glutamic acid [27]. Since then over 100 works dealing with the interactions of AA^P and enzymes appeared, in which over 50 different enzymes were taken into account, in majority the enzymes of metabolic routes of natural amino acids [149, 222]. This inhibition indicates a structural antagonism of AA^P and AA^C, compatible with the fact that many enzymes recognize aminophosphonic acids as similar to corresponding natural amino acids.

The most representative examples of an inhibiting action of AA^P towards enzymes are:

— inhibition of glutamic synthetase [17, 120, 202] and decarboxylase [160];
— inhibition of angiotensin converting enzyme [108, 165];
— inhibition of adenyl-succinate lyase [84];
— inhibition of alanine racemase [83, 152, 154, 164, 170, 183];
— inhibition of L-phenylalanine ammonialyase [157, 159];
— inhibition of tyrosinase [178];
— inhibition of folylopoliglutamate [193].

Structural differences between AA^P and AA^C are not sufficient enough to prevent aminophosphonic acids against substrate function in several enzymatic reactions. A representative example of such an interaction are similarities of 3,4-dihydroxyphenyl-alanine (DOPA) with tyrosinase [178]. The simple replacement of the carboxyl by the phosphonic function in DOPA leads to the analogue $DOPA^P$, which behaves towards tyrosinase as a synthetic substrate. Shortening of the linkage between an amino-phosphonic moiety and an aromatic ring leads to $DHPG^P$, which is one of the strongest inhibitors of tyrosinase.

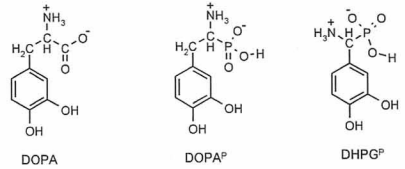
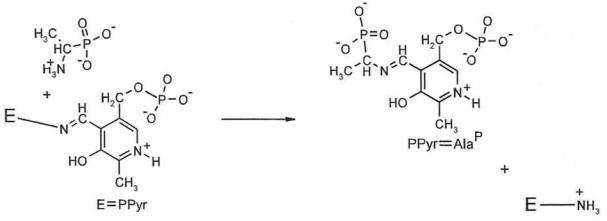


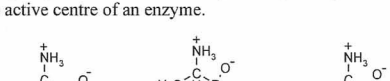
Fig. 3. Structures of DOPA, $DOPA^P$ and $DHPG^P$

Racemases of alanine belong to a group of bacterial enzymes catalyzing the racemization of alanine (L-Ala → D-Ala). These enzymes become active in early stages of the cell growth providing bacterial cells in D-Ala, an essential component of bacterial cellular wall [207]. Therefore, racemases present attractive target in construction of antibacterial drugs. The phosphonic analogue of alanine, Ala^P, is a potential inhibitor of bacterial racemases of the Gram-positive group [152,183]. Mechanism of this inhibition involves the reaction of Ala^P with 5'-phosphate of pyridoxal (PPyr), identical with that of Ala (scheme 58).

Scheme 58



The formed pyridoxal aldimine of inhibitor (PPyr=Ala^{P}), causes bigger change of conformation of the binding enzyme than PPyr=Ala, probably by stronger electrostatic interaction of the phosphonate di-anion with positively charged side chains (Lys, His and/or Arg) of an active centre of an enzyme.



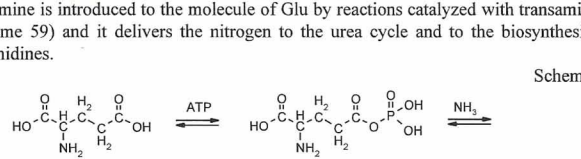
Ala Ala^{P} Ala^{PH}

Fig. 4. Structures of anionic forms of Ala, Ala^{P} and Ala^{PH} present in physiologic solutions

This mechanism is supported by the fact that the phosphinic analogue of alanine (Ala^{PH}) – forming mono-charged anion, does not cause such significant deactivation of the enzyme (Fig. 4).

Glutamine synthetase catalyzes the important reaction of metabolism of nitrogen – i.e. the conversion of glutamic acid to glutamine (Glu → Gln). The amide nitrogen of glutamine is introduced to the molecule of Glu by reactions catalyzed with transaminase (scheme 59) and it delivers the nitrogen to the urea cycle and to the biosynthesis of pyrimidines.

Scheme 59



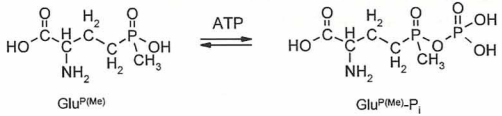
Phosphinothricin (Glu$^{\gamma\text{-P(Me)}}$), the phosphinic analogue of glutamic acid (produced by Streptomyces) [36] is a strong inhibitor of glutamic synthetase (Fig. 5).

Glu Glu^{P} Glu$^{P(Me)}$

Fig. 5. Structures of glutamic acid (Glu), and its phosphinic (Glu $^{\gamma\text{-P(Me)}}$; phosphinothricin) and phosphonic (Glu$^{\gamma\text{-P}}$) analogues

Glu $^{\gamma\text{-P(Me)}}$ is a considerably stronger inhibitor of glutaminase than Glu $^{\gamma\text{-P}}$. Since Glu^{P} (H_3L) exists in physiological solutions as tri-charged (L^{3-}) whereas Glu $^{\gamma\text{-P(Me)}}$ as two-charged anions, this observation suggests that the electrostatic interaction of an inhibitor and enzyme does not constitute a predominant factor of the mechanism of the considered reaction.

Scheme 60



The phosphorylated phosphinothricin Glu $^{\gamma\text{-P}}$-P$_i$ (scheme 60) is the mimetic of a tetrahedral transition state of enzymatic reaction (scheme 59: Glu + ATP + NH_3), and it can be considered as the enzymatically created analogue of the transition state (Fig. 6).

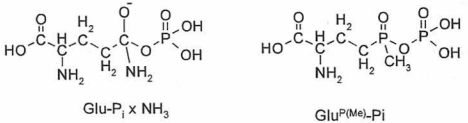


Fig. 6. Structures of hypothetic adduct Glu-P$_i$×NH_3 and mixed phosphinothricin-phosphate anhydride Glu $^{\gamma\text{-P(Me)}}$-Pi

The phosphonic analogues of mixed aminoacyl-phosphate anhydrides AA^C-MPA are another group of the analogues of metabolic intermediates. These isosteric compounds differ from parent metabolites by the presence of a methylene instead of an oxygen bridge of the phosphate group (Fig. 7) [45, 114].

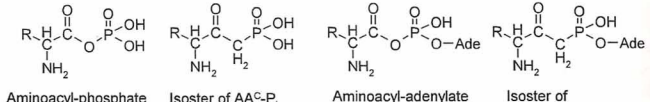
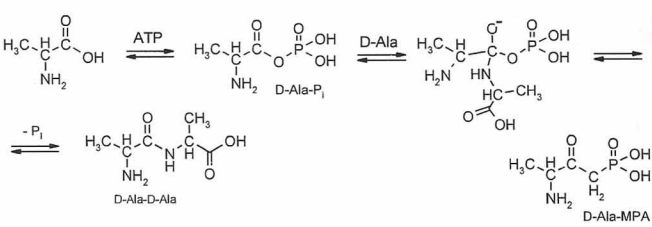


Fig. 7. Structures of aminoacyl-phosphate and aminoacyl-adenylate with their isosters

Scheme 61



The illustrative example of this approach presents the inhibition of D-Ala ligase by Ala-MPA – the phosphonic analogue of D-Ala-P$_i$, the hypothetic intermediate of enzy-

matic synthesis of D-Ala-D-Ala (scheme 61, Fig. 11). This dipeptide is considered as the key precursor of the biosynthesis of bacterial cell wall [198, 215].

4.2. Antibacterial activity [222]

The group of phosphoroorganic antibiotics, particularly phosphonic antibiotics is an interesting, persistently expanding group of antibacterial agents. The first antibacterial aminophosphonic acid – phosphanilic acid, was synthesized by Nijk in 1923 and recognized as an antibacterial species by Baurer in 1941 [222]. This mimetic of p-aminobenzoic and sulphanilic acids (Fig. 9) has a low toxicity and a substantial, comparable with sulphamides efficiency. Slow development in this field before 1970 contrasts with rapid acceleration in recent decades; as a result tens of natural antibiotics were identified and hundreds were synthesized.

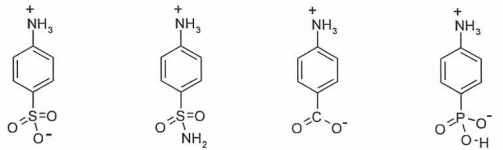


Fig. 9. Structures of sulphanilic acid (PAS), sulphanilamide (SNA), p-aminobenzoic (PAB) and p-phosphanilic (PABP) acids

Discovery of natural antibacterial phosphonopeptides was crowned by the discovery of strongly antibacterial alafosfaline (Ala-Ala^P) [58, 83, 99, 148]. Ala-Ala^P was sorted out from a wide group of phosphonopeptides on the basis of the biological activity, pharmacokinetic profile, and stability in relation to peptidases. Detailed investigations of Ala-Ala^P exhibited its usefulness in clinical treatment of contagions of the urinary tract. The discovery of Ala-Ala^P stimulated an intensive research on synthesis of new phosphonopeptides. As a result a few hundreds of different mixed phosphonopeptides, in majority P-terminal were synthesized, which showed promising activity *in vitro* [140, 148, 234, 279, 285]. Main types of phosphonopeptides are presented in Fig. 10.

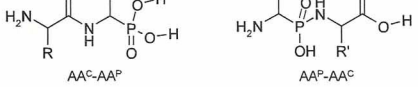


Fig. 10. Structures of mixed phosphono-carboxylic dipeptides

A mechanism of action of phosphonopeptides (synthetic and/or natural), presented for Ala-Ala^P schematically in Fig. 11, includes an active transportation through bacterial cell walls in conjunction with peptydyl-permeases and subsequent enzymatic hydrolysis of the phosphonopeptides to free AA^P inside bacterial cell [131]. Released AA^P reacts with specific enzymes. Thus, Ala^P (released by hydrolysis of Ala-Ala^P) inhibits alanine racemases while phosphinothricin (released from Bialaphos) inhibits glutamic synthetase, thus exerting toxic effects.

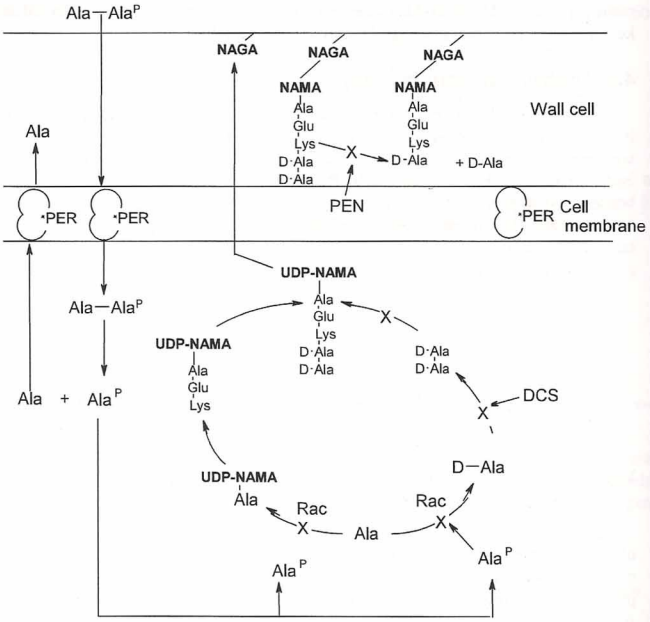


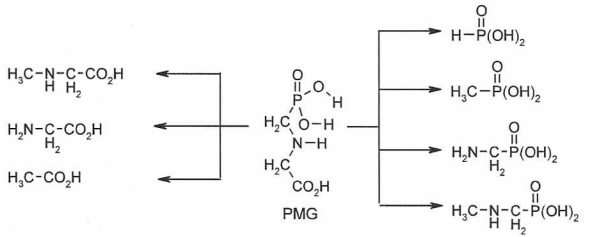
Fig 11. The mechanism of antibiotic action of Ala-Ala^P on a formation of bacterial wall-cell: Rac – alanine racemase; DCS – D-cycloserine; PEN – penicillin; PER – permease; NAMA – N-acetylmuramic acid; NAGA – N-acetylglucosoamine; UDP – uridinediphosphate; UDP-NAMA – uridinediphospate-NAMA subunit

4.3. Activity of control of plants growth [186, 222, 286]

The discovery of herbicidal activity of N-phosphonomethylglycine (PMG) in 1971, made up a milestone in the biochemistry of aminophosphonic acids. This discovery initiated an intensive research works connected with design, synthesis and evaluation of biological proprieties of aminophosphonic acids.

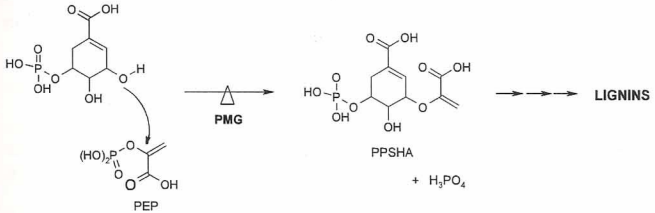
PMG [62] presents remarkably fast and effective, post-emergency herbicide, produced by Monsanto (Roundup), and sold to over 100 countries. Low molar mass and high solubility of PMG in water, allows on its facile absorption and translocation in plant cells. PMG is a non-toxic compound, which does not undergo accumulation in animal cells and is easily degraded in environment to non-toxic products (scheme 62).

Scheme 62



PMG shows its herbicidal activity by inhibition of 5-enolopyruvylshikimic-3-phosphate synthetase, blocking the shikimate pathway acid (scheme 63) and indirectly a synthesis of lignins, responsible for hardening of grassy stems.

Scheme 63



PEP: phosphoenolpyruvate; PSHA – phosphoshikimic acid; PPSHA – phosphopyruvylshikimic acid

The discovery of herbicidal activity of PMG stimulated an intensive development of research programs, directed on synthesis of AA^P possessing potential biological properties. As an effect, hundreds of PMG analogues were synthesized and applied for subsequent biochemical tests. These data are the topic of a number of various patent-reports. The structures of representative aminophosphonic herbicides are presented in Table 2.

5. Conclusions

The key role of naturally occurring amino acids in chemistry of life as structural units in peptides, proteins and enzymes, has led to intense interest in the chemistry and biological activity of their synthetic analogues. Aminophosphonic acids – so-called "phosphorous analogues" of the amino acids, in which the carboxylic group is replaced by the phosphonic group, are in majority anthropogenic compounds (excluding β-Ala^P, $Asp^{\beta\text{-}P}$, Tyr^P and $Iser^P$) [136, 149]. These compounds have attracted particular interest

and have reached an important position in research aiming to the discovery, understanding, and modifications of physiological processes in living organisms [273].

In addition, AA^P and their derivatives are of interest as metal-complexing agents which may control the uptake or removal of metal ions in living systems, and have numerous diagnostic and therapeutic applications [26, 53, 145, 282].

The generally low mammalian toxicity of AA^P makes them attractive for use in medicine and agriculture, and a number of important applications in these areas are now well established [273].

The replacement of carbon by phosphorous has many consequences, which are important for the behavior of the AA^P, compared to that of the corresponding AA^C. The tetrahedral configuration of phosphorus is valuable for the design of transition state-analogue enzyme-inhibitors, which have wide-range potential in medicinal applications (inhibition of HIV protease, thrombin, human collagenase, therapeutic use in the treatment of disorders of the central nervous system, treatment of bone disorders, anti-cancer and antiviral activities) [273].

A variety of applications and possible use of AA^P as industrial chemicals, e.g. in water treatment, as sequestering agents, and in pollution control and metal extraction [28, 273, 294] are very promising. The further development of organophosphorus chemistry in these directions will open new possibilities for the practical applications of these compounds.

6. Literature

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Zbigniew H. Kudzin

KWASY 1-AMINOALKANOFOSFONOWE: SZEŚĆ DEKAD BADAŃ

Streszczenie: Omówiono kwasy 1-aminoalkanofosfonowe (AA^P) pod względem ich syntez, właściwości fizykochemicznych i aktywności biologicznej.

Pierwsza część, dotycząca syntez AA^P, składa się z siedmiu działów, w których podano stosowane metody; w drugiej części opisano wyniki spektroskopii UV i NMR, oraz chelatujące właściwości AA^P. W trzeciej części scharakteryzowano AA^P jako inhibitory enzymów oraz opisano ich aktywność biologiczną.