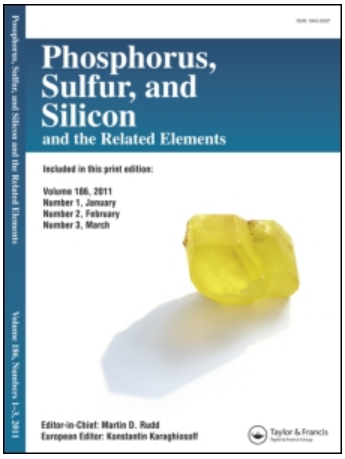

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Synthesis and Properties of Aminophosphonic Acids and Phosphonopeptides

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SYNTHESIS AND PROPERTIES OF AMINOPHOSPHONIC ACIDS AND PHOSPHONOPEPTIDES

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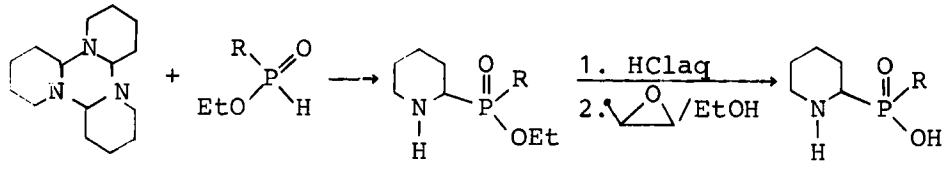
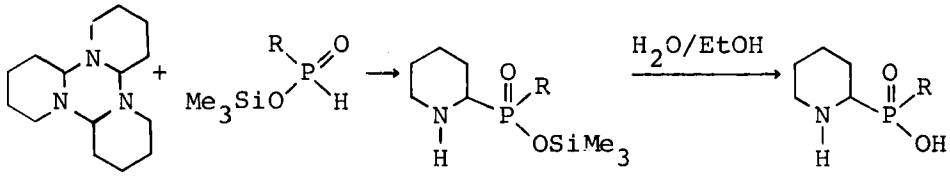
In recent years phosphorous analogues of amino acids (aminophosphonic, aminophosphinic and aminophosphonous acids) have attracted growing attention of investigators. Among these compounds are the first natural ones containing P-C bond and produced by living organisms.[1] As mimetics of natural amino acids they are potential bioregulators. These compounds were found to be substrates and inhibitors of enzymes, to possess plant growth regulating and herbicidal properties, to display antibacterial, antitumoral and neuronal activities.[2] Studies of aminophosphonic and aminophosphinic acids (APA) in our laboratory have been directed towards development of APA synthesis methods, obtaining of new APA, investigation of their properties, evaluation of structure-bioactivity relations and design of APA-based low-molecular bioregulators. The chemical aspects of our studies are described here.

There is quite a large number of methods for APA synthesis. Some of these methods are general, others are applicable only for synthesis of certain APA.[3] We have worked out the method of synthesis of phosphonic and phosphinic analogues of natural iminocarboxylic acid homoproline. The method is based on iminoalkylation of dialkyl phosphites or monoalkyl alkyl(aryl)phosphonites with trimer of 2,3,4,5-tetrahydropyridine.[4] Hydrolysis of the adducts formed in acidic medium (boiling with concentrated HCl) leads to the hydrochlorides of phosphorus analogues of homoproline from which free acids were isolated by treatment with propylene oxide or by ion-exchange chromatography.



Localization of phosphorus moiety in α-position of these compounds is confirmed by ^{13}C NMR spectra showing downfield doublets of C_α with δ_C 55-58 ppm and $^1J_{PC}$ 88-141 Hz. As the isolation of free iminophosphonic and iminophosphinic acids from their hydrochlorides is difficult, it was of interest to by-pass the procedure. For this aim the trimethylsilyl esters of phosphorous and phosphonous acids were used instead of alkyl esters in reaction with the trimer of tetrahydropyridine. The hydrolysis of produced silyl phosphonate and silyl phosphinates proceeds easily under neutral conditions (10-20-min. heating with aqueous alcohol). Application of such approach facilitates the isolation of the products and increases their yields.

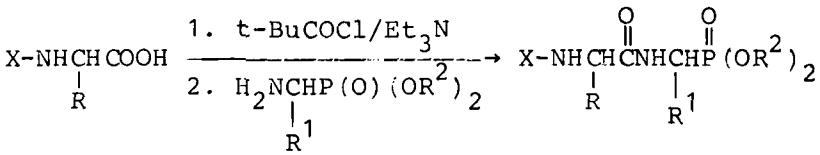


Some properties of phosphorous analogues of homoproline were investigated. For piperidine-2-phosphonic acid the pK_1 = 2.0, pK_2 = 5.74, and pK_3 = 11.31 were determined. This acid was found to form stable complexes with transition metals; the lg K_{MA} determined by potentiometric method equals to 5.10 for Co^{2+}, 5.89 for Ni^{2+}, 8.76 for Cu^{2+}, and 5.86 for Zn^{2+}. The most stable complex is formed with zirconium. It allowed to introduce piperidine-2-phosphonic acid as chelating ligand for the determination of microquantities of zirconium.[5]

Considering APA as the objects of bioorganic chemistry, stereochemical aspects become of great importance. Optically active 1-aminoethylphosphonic acid (this compound is known to be effective inhibitor of alanine racemase) was

obtained by traditional methods of racemate separation with dibenzoyl-L-tartaric acid, but yields of the product were moderate or low. To overcome this problem we paid attention to enzymatic methods of racemate separation. We synthesized a number of APA derivatives, which can serve as substrates of hydrolytic enzymes and tested their properties. Optically active phosphonic analogues of alanine, leucine, phenylglycine and phenylalanine were obtained in high yields and showed excellent optical purity. Results of this study are discussed.

Aminophosphonic acids can be used as components in peptide synthesis. Phosphonopeptides produced exhibit promising bioactivity.[2] A number of methods of phosphonopeptide synthesis has been developed in recent years. We have found that esters of 1-aminoalkylphosphonic acids react readily with mixed anhydrides of N-protected amino acids and pivalic acid to give the totally protected phosphonopeptides.



Till now only chemical methods of phosphonopeptide synthesis were known. We have found that phosphonopeptides can be obtained by the enzymatic route using papain as the catalyst.[6] The reactions were carried out in organic solvent with minimal water content, the enzyme was immobilized on the polyamide carrier. Under these conditions phosphonopeptides with P-terminal aminophosphonic acids were obtained in good yields. The process was found to proceed stereoselectively in regard to racemic amino component: mainly L-aminophosphonate is involved in the peptide bond formation. The elaborated method was applied for synthesis of bioactive phosphonopeptide alafosfalin. The advantages and scope of this method are discussed.

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