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Nucleophilic substitution at phosphorus: stereochemistry and mechanisms

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Dedicated to Professor Dr. M. Mikołajczyk (Lodz, Poland) on the occasion of his 80th birthday

ABSTRACT

This review is devoted to the stereochemistry of nucleophilic substitution reactions at phosphorus. The study of the reactions of phosphoryl group transfer is important for biological and molecular chemistry. The stereochemistry and mechanisms of $S_N1(P)$ monomolecular and $S_N2(P)$ bimolecular nucleophilic substitution reactions of organophosphorus compounds are discussed. It has been shown that hydrolysis of many natural phosphates proceeds according to the monomolecular $S_N1(P)$ mechanism via the formation of metaphosphate intermediate (PO_3^-). $S_N2(P)$ nucleophilic substitution at chiral trivalent or pentavalent phosphorus compounds proceeds via the formation of penta-coordinated transition state or pentacoordinate intermediate.

Contents

Abbreviations: Ac, acetyl; An, anisyl; Ar, aryl; ATP, adenosine triphosphate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; Bz, benzoyl; cat, catalyst; conv, conversion; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DMF, *N*,*N*-dimethylformamide; dmpe, 1,2-bis (dimethylphosphino)ethane; DMSO, dimethylsulfoxide; EA, elimination–addition; ee, enantiomeric excess; Et, ethyl; Fmoc, 9-fluorenylmethoxycarbonyl; Fu, furanyl; GF1, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone D-glucose); GF2, I.2:5.6-Di-*O*-cyclohexylidene-α-D-glucofuranose; Hex, hexyl; L, Lig, ligand; Me, methyl; Mes, mesyl; Mnt, (1*R*,2*S*,5*R*)-menthyl; MTBE, methyl *tert*-butyl ether; nphth, naphthyl; Oct, octyl; Pent, pentyl; Ph, phenyl; Piv, pivaloyl; Pr, propyl; py, pyridyl; TADDOL, a,a,a0,a0-tetraaryl-1,3-dioxolane-4,5-dimethanol; TBAB, tetra-*n*-butylammonium bromide; TBP, bipyramidal intermediate; TBS, *tert*-butyldimethylsilyl; TC, transition complex; THF, tetrahydrofuran; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; TMS, trimethylsilyl; Tl, tolyl; Ts, 4-toluenesulfonyl (tosyl); TS, transition state.

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1. Introduction

The most frequently encountered reactions in organic phosphorus chemistry are nucleophilic substitution reactions ($S_N(P)$). The mechanism and stereochemical course of S_NP reactions have been intensively studied. In the overwhelming majority of cases S_N2 nucleophilic substitution at the chiral tricoordinate trivalent phosphorus results in the inversion of configuration that assumes the formation of pentacoordinate intermediate, containing attacking and leaving groups in apical positions. Nucleophilic substitution reactions at phosphorus has attracted keen interest because of their important theoretical and practical importance.[1,2] The S_N1(P) and S_N2(P) reactions due to the specific nature of the electronic structure of phosphorus differ from the analogous reactions of nucleophilic substitution at a carbon atom. In contrast to carbon, the phosphorus has d-vacant orbitals, consequently the coordination numbers of phosphorus can increase to 5 or 6! This determines the essential difference in the structure of intermediates and the course of nucleophilic substitution reactions at these elements.

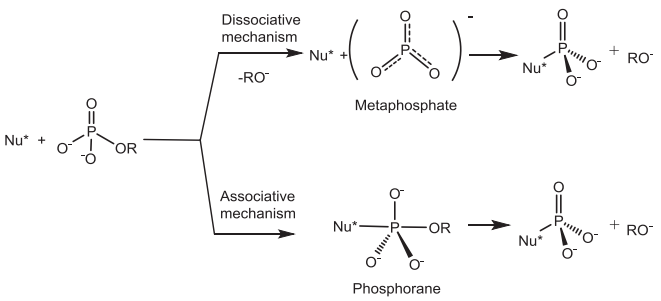
The asymmetric nucleophilic substitution allows various P-chirogenic organophosphorous compounds to be obtained which are widely used in modern chemistry as ligands with complexes with transition metals and also as biologically active compounds, drugs and agrochemicals. The study of transfer reactions of the phosphoryl group is important for biological and molecular chemistry.[3–5] For example, the hydrolysis of ATP takes place in ATPase enzymes through an intermediate in which ATP phosphate is connected to the protein as metaphosphate (PO_3). The theoretical quantum-chemical researches of this nucleotide in natural phosphates have allowed how enzyme stabilizes this unusual metaphosphate to be established.[6–9] The chemical problem discussed in this article involves one of the most important fundamental types of reactions—S_N1(P) and S_N2(P) nucleophilic substitution at phosphorus centers. We discuss the basics of this type of reaction with a selected number of references to the literature. Previously, a full review article examining different types of nucleophilic S_N1(P) and S_N2(P) reactions at the tri- and pentavalent phosphorus atoms, including the stereochemistry of these reactions, has not been published. Though we have recently published a short preliminary report on the stereochemistry of the bimolecular S_N2 nucleophilic substitution at the trivalent phosphorus atom.[10]

2. Monomolecular nucleophilic substitution S_N1(P)

In the chemistry of phosphorus, the monomolecular, and bimolecular reactions of nucleophilic substitution at the phosphorus atom, S_N1(P) and S_N2(P), are well-known. The S_N1(P) reactions participate in the processes of genetic inheritance through nucleic acids and the chemical energy generation that allows the thermodynamically unfavorable processes required for the construction of living cells to be stimulated. The study of the mechanism for the transfer of phosphoryl groups in natural phosphates is important for understanding the basic metabolic pathways and for the cellular signal transduction of fundamental processes in living systems.

There are the following mechanisms for the transfer of phosphoryl groups in the substitution reactions at the phosphorus atom (Scheme 1):[11,12]

(a) dissociative S_N1-type mechanism that involves the formation of a stable metaphosphate ion (PO_3), which is attacked by a nucleophile in the subsequent, rate limiting step;
(b) associative, two-step addition–elimination mechanism through the formation of a phosphorane intermediate.



Scheme 1. Mechanisms of phosphoryl group transfer in substitution reactions at phosphorus atom.

2.1. Metaphosphate intermediate

The mechanism of the ATP hydrolysis reaction, proceeding through the formation of a metaphosphate intermediate, was reported by Westheimer in 1955 (Scheme 2).[13] A dissociative method of breaking the P—C bond to form a metaphosphonate intermediate is observed in the case of sterically hindered phosphorus compounds, most often in weakly nucleophilic solvents. Pentavalent three-coordinated metaphosphate is very reactive in aqueous solutions. Therefore, it cannot be registered in aqueous solutions because of an insignificant lifetime under these conditions. However, metaphosphate can be detected in highly polar and weakly nucleophilic non-aqueous media.[14–18] Besides the metaphosphate–anion PO_3 exists in a stable form in the gas phase and was recorded by various physical methods, first of all by mass spectroscopy.[19] In a gas phase metaphosphate has rather low-reactivity. The enthalpy of deprotonation of HPO_3-in the gas-phase is only 314 kcal/mol. Metaphosphate-anion was registrated in mass spectra of various pesticides, in products of ionization cleavage of phosphates, in mass spectra of adenosine-5′-monophosphate, in various phosphatriesters, etc.[19] The metaphosphate ion was detected by X-ray crystallographic analysis in some biological molecules in the form of a particle stabilized by coordination bonds, for example in the fructose-1,6-bisphosphatase.[20–24] The crystals of fructoso-1,6-bisphosphatase were grown up in an equilibrium mixture of substratum and product in almost atomic resolution (1,3 Å) (Fig. 1).[17,22]

A metaphosphate ion was also found in the structure of α-phosphoglucomutase (α-PGM) from *Lactococcus lactis* obtained at cryogenic temperatures.[23] Metaphosphate anion, PO_3^- was intensively studied as an intermediate in the aqueous hydrolysis of phosphates.[13,24] The stereochemistry of S_N1(P) reaction proceeding via the formation of metaphosphate-intermediate was studied on the example of phosphates bearing isotopes of oxygen. This allowed the mechanisms of phosphate transfer in solutions and also in active centers of enzymes by physical and chemical methods, using ^{18}O kinetic isotope effect, the linear relations of free energy, stereochemistry methods of ^{16}O, ^{17}O, ^{18}O labeled chiral phosphorus compounds, vibration spectroscopy and also theoretical calculations.[7,16,17] This research allowed the unusual stereochemistry of a methanolysis with participation of metaphosphate anion on the basis of the dissociative S_N1(P) mechanism.[25–27] In the case of the methanolysis of phenylphosphate monoanion **1** (Scheme 3) and dinitrophenyl phosphate dianion **2** (Scheme 4) using [(*R*)-^{16}O, ^{17}O, ^{18}O]-phosphocreatine the full inversion of a configuration at the phosphorus center was observed. It was found that metaphosphate intermediate in proton solvents does not leave the solvation cage in which it was generated and then entered into a further reaction, that creates conditions for the asymmetric reaction (Fig. 2).[25,29]

In the case of phenolic esters having pK_a >5.5, the preliminary protonation equilibrium allows heterolysis to generate metaphos-