



# Main-chain poly(phosphoester)s: History, syntheses, degradation, bio- and flame-retardant applications



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## ABSTRACT

Nature on planet earth is dominated by poly(phosphoester)s (PPEs). They structure and determine life in the form of deoxy- and ribonucleic acid (DNA & RNA), and, as pyrophosphates, they store chemical energy in organisms. Polymer chemistry, however, is dominated by the non-degradable polyolefins and degradable polycarboxylic esters (PCEs) produced on a large scale today. Recent work has illustrated the potential of PPEs for future applications beyond flame-retardancy, the main application of PPEs today, and provided a coherent vision to implement this classic biopolymer in modern applications that demand biocompatibility and degradability as well as the possibility to adjust the properties to individual needs. This comprehensive review summarizes synthetic protocols to PPEs, their applications in biomedicine, e.g., as biodegradable drug carrier or in tissue engineering, and their flame retardant properties. We highlight recent developments that may make phosphorus-based polymers attractive materials for various future applications.

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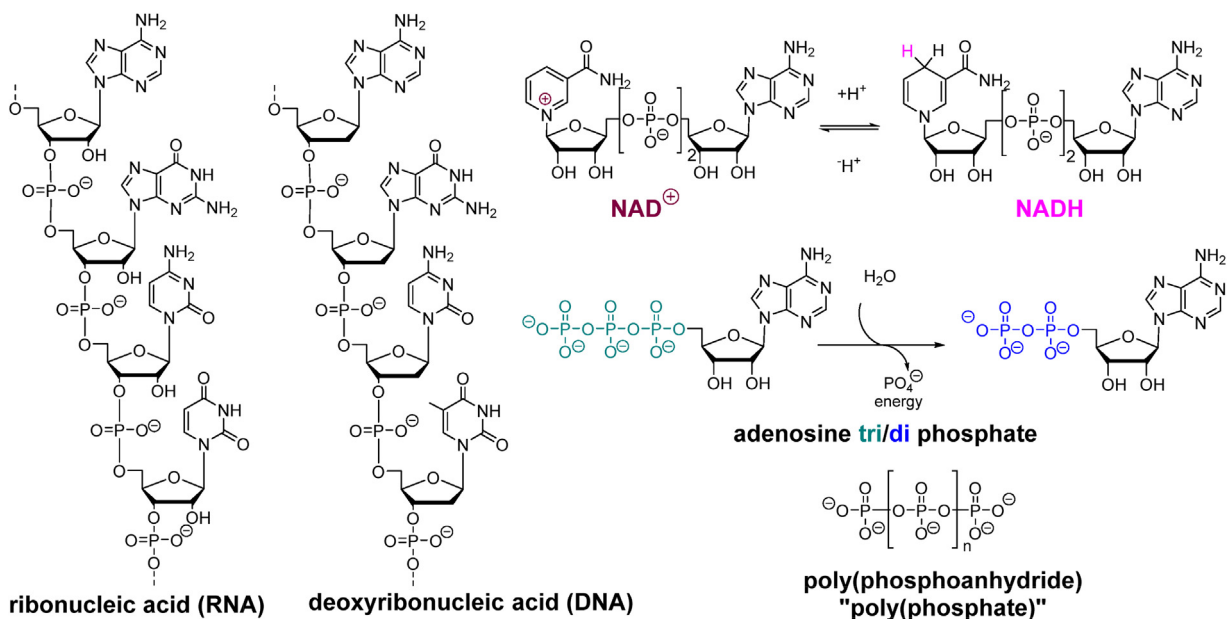
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## 1. Introduction

Poly(phosphoester)s (PPEs), i.e., polyesters based on phosphoric acid derivatives, are omnipresent in nature and all living cells.

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**Fig. 1.** Chemical structures of important phosphorus-containing biomolecules: DNA and RNA sequences, nicotinamide adenine dinucleotide (NADH/NAD<sup>+</sup>) redox pair containing a diphosphate; adenosine tri/di phosphate (ATP and ADP), essential for the energetic flow in living systems; poly(phosphoanhydride) or inorganic polyphosphate, which is found in platelets.

All life relies on the ability of the C–O–P bond to be stable for a long time, but eventually being degradable on demand [1]. The energy-rich phosphorus anhydrides are nature's universal energy storage in the form of adenosine triphosphate (ATP). Controlled cleavage of this bond provides energy for most biochemical reactions. This structure was conserved throughout evolution in all prokaryotes and eukaryotes. Structurally similar but essential for redox-driven bioprocesses, the nicotinamide adenine dinucleotide (NAD<sup>+</sup>/NADH + H<sup>+</sup>) redox system also carries a diphosphate (Fig. 1). Here, a diphosphate is used to link two functionally different parts of a larger molecule together to form a functional unit used in electron transfer processes. Also inorganic polyphosphates play an important role in blood coagulation, inflammation, and bone regeneration [2,3]. Inorganic polyphosphate is structurally very simple, consisting of linear polymers of orthophosphate linked by high-energy phosphoanhydride bonds (Fig. 1). At physiological pH, each internal phosphate unit carries a monovalent negative charge. It is ubiquitous in biology and can vary in polymer length from just a few phosphates to several thousand phosphate units long, depending on the organism and the tissue in which it is synthesized [4].

PPEs differ from these inorganic polyanhydrides by the organic linker between the phosphorus centers; PPEs can be trivalent, i.e., not charged, or divalent (poly(phosphodiester)s) with a negative charge (see below). The most prominent and by far most important examples are the ribonucleic acids and their polymeric forms, DNA and RNA. These macromolecules, as PPEs, encode the genetic information of life and are essential for higher and lower life forms. Both RNA and DNA are PPEs built up from phosphoric acid and derivatives of the carbohydrates ribose or desoxyribose (with the additional nucleobases attached to the anomeric centre), respectively (Fig. 1).

The negatively charged phosphorus diester in DNA (in combination with the helical double stranded structure) provides long term stability as nucleophilic attacks are unlikely to the anionic charge of the backbone. As natural motif different enzymes are capable of building or degrading phosphoesters. In contrast to DNA, RNA is hydrolyzed much faster, due to the proximity of the additional OH-group on ribose, catalyzing the rapid depolymerization of RNA. The negative charge on the phosphate moiety further allows for interac-

tions with positively charged proteins, the most well-known being histone proteins. These are used for storage and stability purposes [5]. A reduction in positive charge of these proteins plays an important role in the exposing of DNA for other protein-like transcription or translation factors [5].

Phosphorylation is a general pathway to regulate enzyme activity in cells and hence a multitude of enzymes, the phosphatases, are known with the sole purpose of cleaving several differently substituted phosphoesters [5]. Also, synthetic phosphoesters are expected to be enzymatically degraded inside a living system in addition to the intrinsic susceptibility of ester bonds towards (acidic or basic) hydrolysis. Besides phosphates (i.e., with the structural element PO<sub>4</sub><sup>3-</sup>), also phosphonates (carrying one stable P–C bond, i.e., PRO<sub>3</sub><sup>2-</sup> (Fig. 4)), are important structural elements in nature. Phosphonic acid derivatives have been identified in various plants, fungi, bacteria, and in some animals [6]. Recent <sup>31</sup>P NMR spectroscopic studies proved that up to 30% of the maritime phosphorus reserve is bound in phosphonic acid derivatives [7]. Also many herbicides, such as the currently heavily discussed glyphosate, are based on phosphonates.

The omnipresence and immense biological importance of phosphoric acid esters makes synthetic PPEs a very promising object of research. These polymers are expected to show a high compatibility with biological systems and potentially low toxicity. Compared to the polyesters based on carboxylic acid esters, phosphorus, in phosphoric acid, can form three stable and divergent bonds in addition to the P=O double bond. This makes not only poly(phosphoester)s, but also and the respective amides, a versatile platform for main- and side-chain modification of synthetic polymers, a distinct advantage over carboxylic acid esters, for example (Fig. 2) [8]. Attachment of side-chain functionalities and labels and therefore modification of material properties is possible in a straightforward way via the pendant group. This avoids main-chain functionalization that has to be conducted for other polycarboxylic acid esters or amides, e.g., in functional lactones or lactams. Also the intrinsic biodegradability of PPEs can be adjusted via side-chain (and main-chain) modifications [9].

Polymer chemists have always taken motifs from nature to synthetics (Fig. 3). Polyolefins became a commodity material for the

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