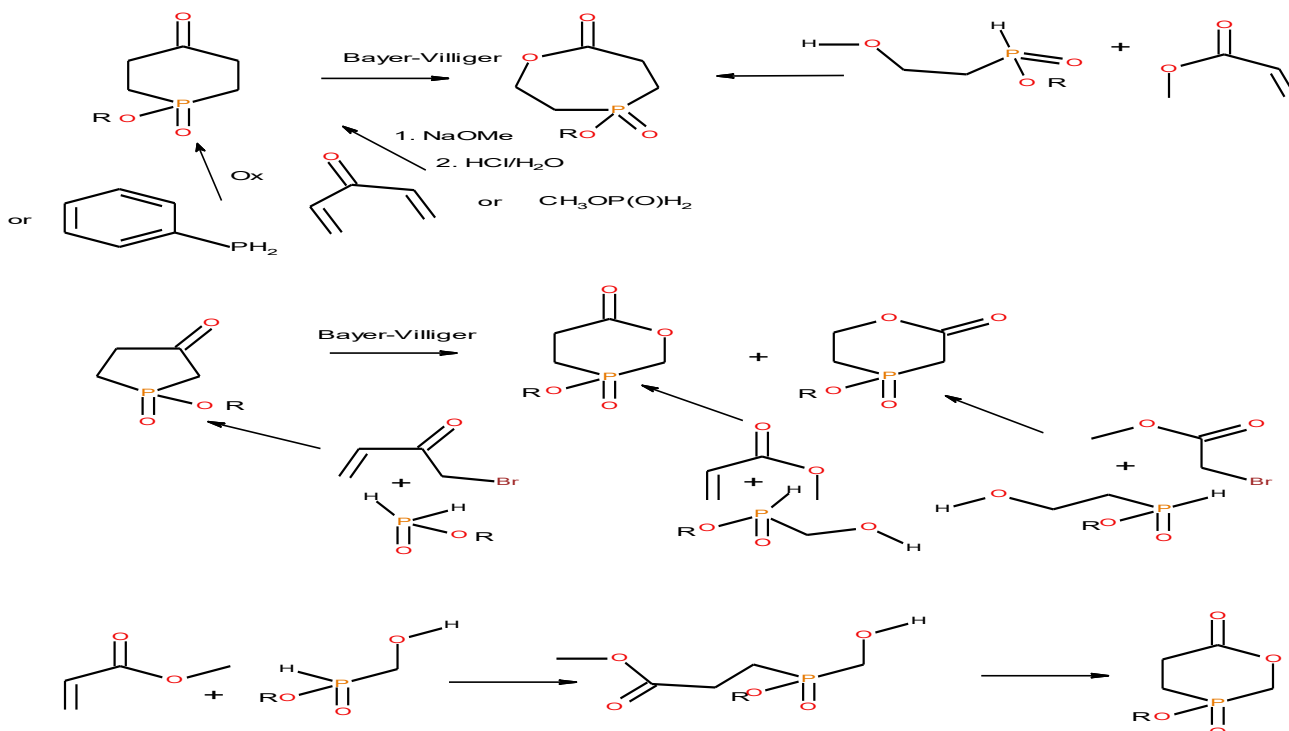


Phosphorus Containing Specialties

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ROP of Phosphinate Lactam or Lactone Heterocyclic Monomers

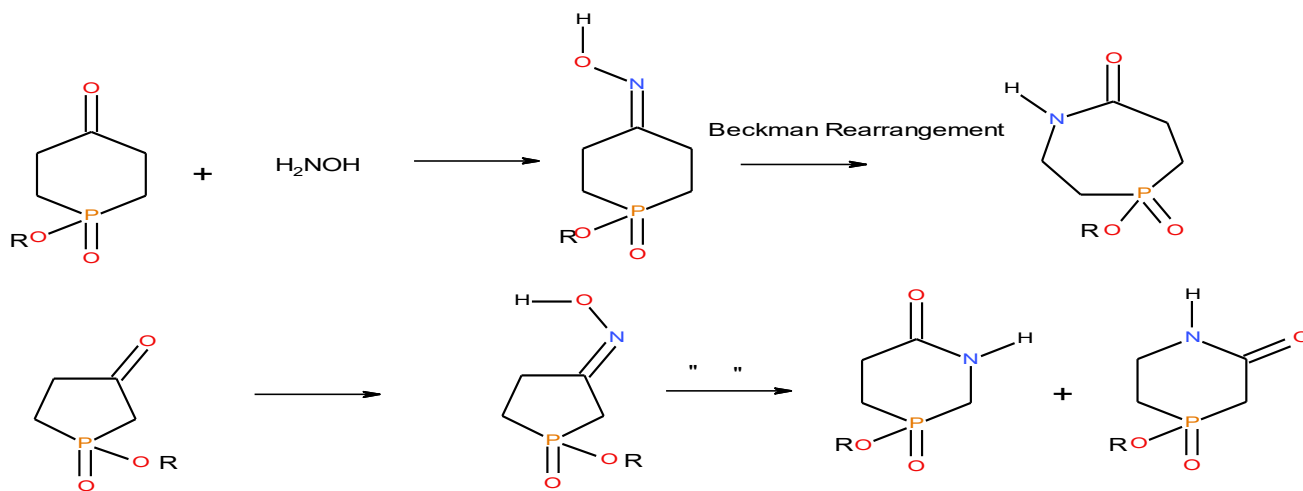
Polyphosphoesters prepared by ROP or by condensation produce valuable polyesters are of great importance to medical science, biotechnology and technology in general. A recent book on the subject written by K. D. Troev, a noted authority, reviews their chemistry (Phosphoesters, Chemistry and Applications; Elsevier, 2012). I refer you to this excellent review. Rather than polymerizing a phosphorus monomer by what ever means, why not use another polymerizable moiety such as a caprolactone or lactam the also contains non-polymerizable phosphorus in the heterocycle. This would allow the resulting polymer to contain the phosphorus derivative in the backbone where its further chemistry could be employed for derivatising or xlinking. In addition, such monomers would also be readily copolymerizable with other caprolactone or lactams or other ROP monomers, conveniently with the same catalyst systems.



Scheme 1

Scheme 1 illustrates in outline form suggested synthetic pathways to these monomers.

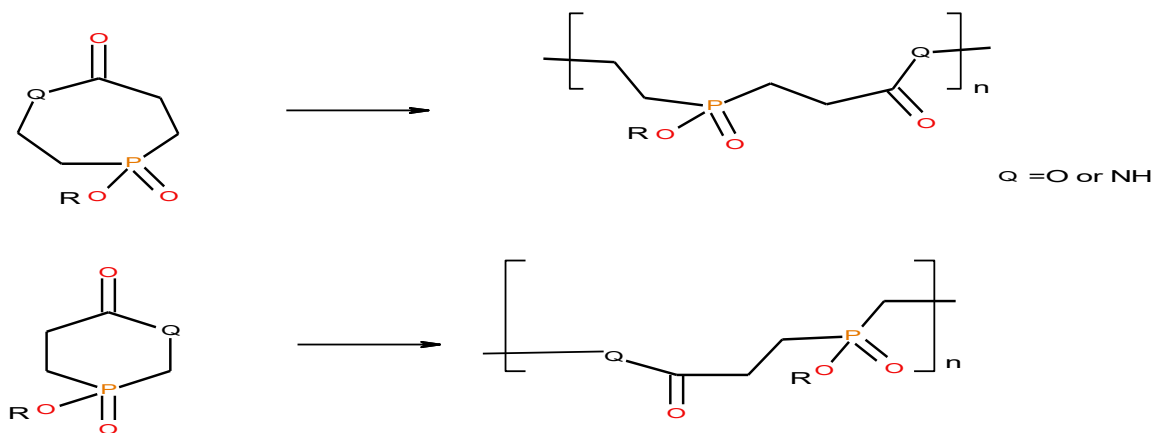
Details of this type of phosphinate chemistry can be found in various articles written by J. L. Montchamp (<http://personal.tcu.edu/jmontchamp/Research%20Highlights.pdf>). (1-6)



Scheme 2

Scheme 2 illustrates synthesis of potential phospholactams. This chemistry has been described in the 1970's (Shalaby, S. W., et al. "Synthesis and polymerization of 1, 5-dioxo-1-methyl-4-

azaphosphepane." *Journal of Polymer Science: Polymer Chemistry Edition*, 12.12 (1974): 2917-2925.)



Scheme 3

Scheme 3 illustrates the ROP of the suggested monomers. I believe these monomers besides forming homopolymers, can be copolymerized with a wide variety of ROP monomers (7-9).

Other oxidation states of phosphorus besides phosphinates such as phosphines or phosphine oxide should also be considered. Since phosphorus has the ability to be derivatised depending on the oxidation state, medically important derivatives may require the chemistry of said other oxidation states(10).

References:

1. Berger, Olivier, and Jean-Luc Montchamp. "Phosphinate-containing heterocycles: A mini-review." *Beilstein journal of organic chemistry* 10.1 (2014): 732-740.
2. Montchamp, Jean-Luc. "Phosphinate chemistry in the 21st century: a viable alternative to the use of phosphorus trichloride in organophosphorus synthesis." *Acc. Chem. Res* 47.1 (2014): 77-87.
3. V Salin, Alexey, et al. "The Pudovik reaction catalyzed by tertiary phosphines." *Current Organic Synthesis* 13.1 (2016): 132-141.
4. Fisher, Henry C., Lucie Prost, and Jean-Luc Montchamp. "Organophosphorus Chemistry without PCl_3 : A Bridge from Hypophosphorous Acid to H-Phosphonate Diesters." *European Journal of Organic Chemistry* 2013.35 (2013): 7973-7978.
5. Hewitt, DAVID G. "Six-membered rings with one phosphorus atom." *Comprehensive Heterocyclic Chemistry II*; 5 (1996).
6. Quin, Louis D.; *heterocyclic chemistry of phosphorus*. Wiley, 1981.
7. Nuyken, Oskar, and Stephen D. Pask. "Ring-opening polymerization—an introductory review." *Polymers* 5.2 (2013): 361-403.
8. Stridsberg, Kajsa M., Maria Ryner, and Ann-Christine Albertsson. "Controlled ring-opening polymerization:

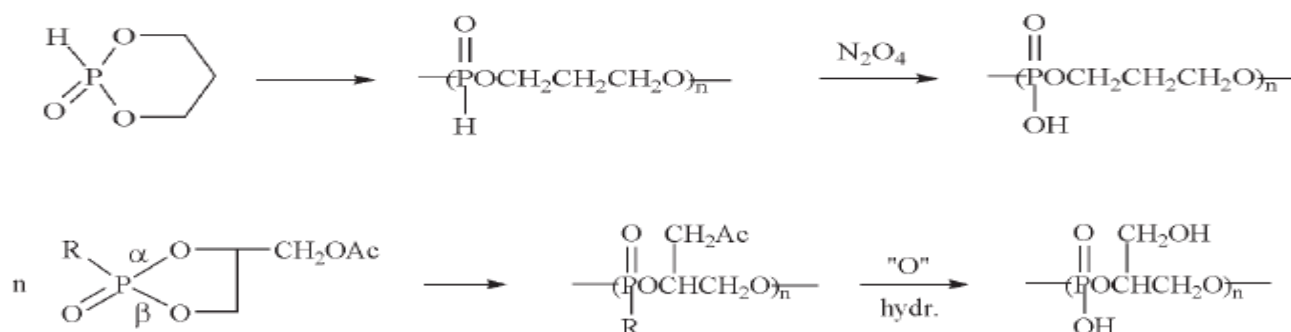
polymers with designed macromolecular architecture." *Degradable aliphatic polyesters.*"; Springer Berlin Heidelberg, 2002. 41-65.

9. Labet, Marianne, and Wim Thielemans. "Synthesis of polycaprolactone: a review." *Chemical Society Reviews*; 38.12 (2009): 3484-3504.
10. Bauer, Kristin N., et al. "In-Chain Poly (phosphonate) s via Acyclic Diene Metathesis Polycondensation." *Macromolecules*; 49.10 (2016): 3761-3768.

Polyphosphonate Hydrogels

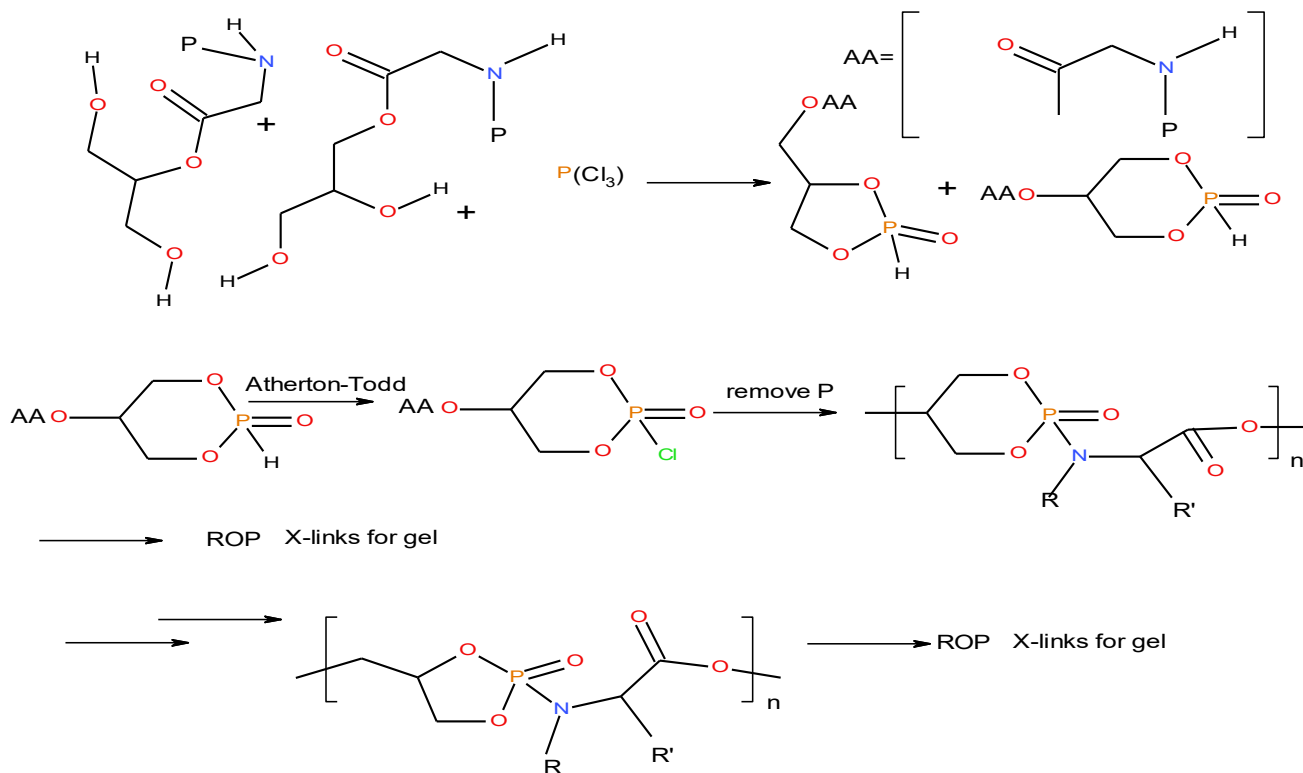
The usual approach to water soluble polyphosphonates is to prepare them by transesterification of phosphonate esters with diols or by ring opening polymerization (ROP) and then to derivatise the resulting polymers by Atherton-Todd or other reactions. Polyphosphonates or phosphates are readily (bio)degradable because of the phosphorus ester linkage. This has led to numerous papers and patents describing medical and dental applications such as drug delivery, DNA carrier, tissue engineering etc.. because of the ability to derivatise the resulting polymers for such applications. Post polymerization xlinking is also of interest as degradable hydrogels would result. There is a significant literature concerning these polymers (1-4).

For example:



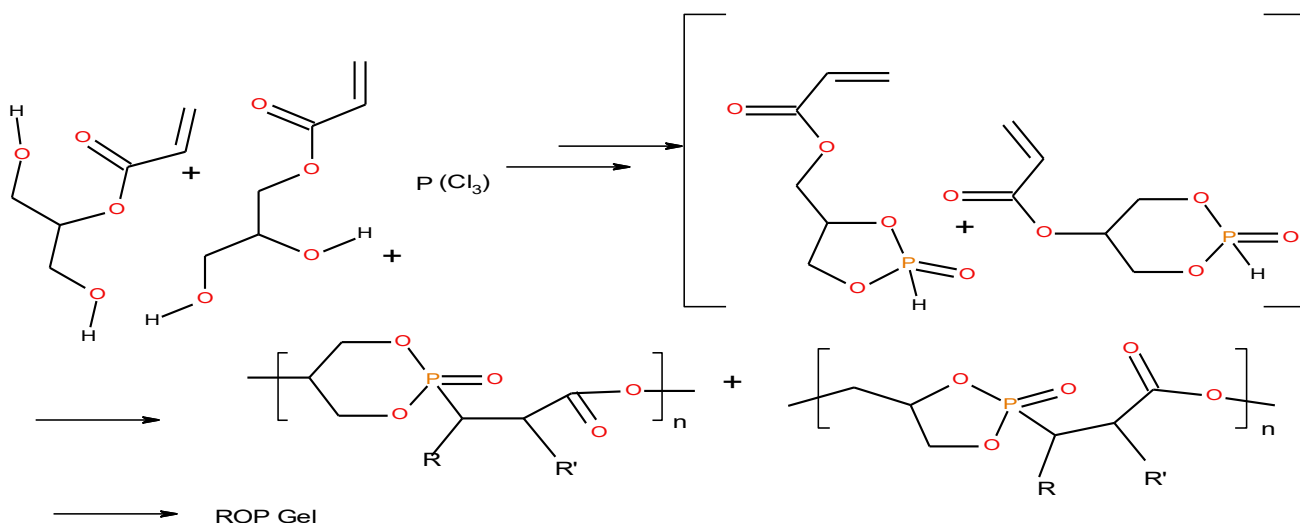
ROP starts with an initiating alcohol and a metal containing catalyst; however, presently very basic compounds like DBU can be used avoiding heavy metal toxicity. The above

schemes show conversion of the polyphosphonates to polyphosphates because the phosphates are more hydrolytically stable. The above polymer R-groups or hydrogen can also be chloride which can be prepared in a variety of ways (Atherton-Todd reaction for example). My first proposal is shown in scheme 1.



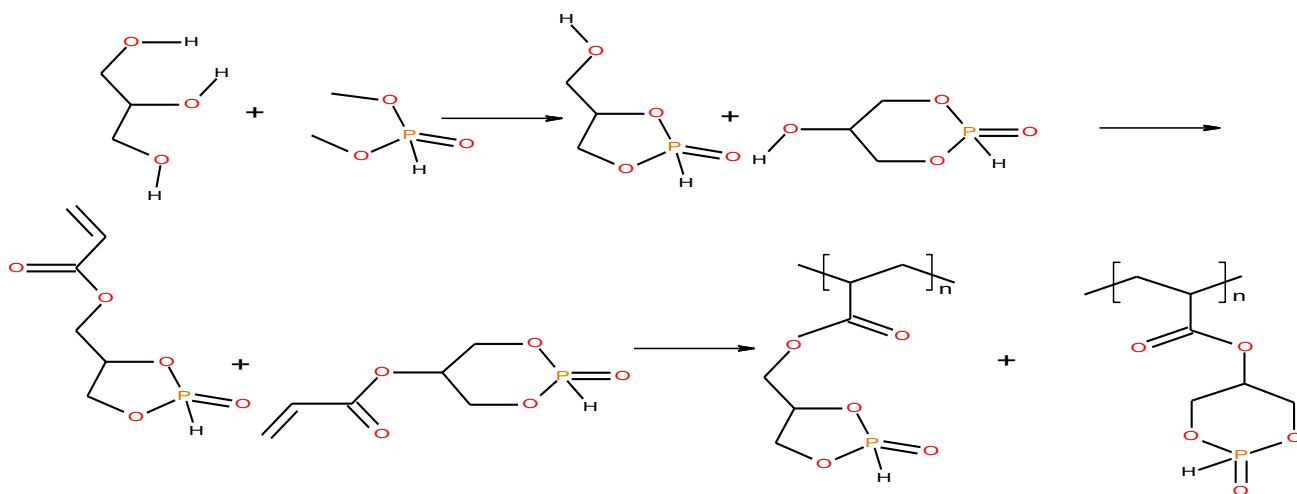
Scheme 1 (P=protected amine group); AA=amino acid or peptide group

The idea is to form a polymer that contains the cyclic phosphoramidate that can be post polymerized with a strong base like DBU to form xlinks. The xlinked product would be hydroscopic and form a hydrogel as it absorbs water. The entire hydrogel would eventually degrade to phosphoric acid, glycerol, and amino acids or peptides. As the hydrogel degrades it could release medicinals and be a unique drug carrier with innocuous by-products. Furthermore, if the peptide used is designed to be an active drug in its own rite, then this would also be a valuable delivery mechanism for it. The reactions described in scheme 1 are based on known chemistry. (5-6)



Scheme 2

Scheme 2 proposes that mono-acrylate esters would undergo the Pudovik(7) (Michael) reaction to form a polyester containing as before, a phosphonate ROP post polymerizable monomer that would afford crosslinking. (It is conceivable that PCl_3 could first do a Pudovik (Michael) reaction on the glycerol acrylate ester and subsequently forming the polymer containing the 1,3,2-dioxaphosphorinanes, the reverse of what's shown in scheme 2.) Hydrolysis should be enhanced by the phosphorus carboxylate ester oxygen interaction as its in a favorable five position vs the ester. Here again innocuous byproducts would eventually result from hydrolysis, so that long term toxicity problems should be eliminated.



Scheme 3

Scheme 3 employs acrylate or other FR polymerizable monomers. While this approach results in polymers that do not completely degrade, it still is in the same vein as the other schemes. The idea of employing heterocyclic ROP phosphorus monomers to xlink the resulting polyacrylate polymer.

In conclusion, under anhydrous conditions, the above xlinkable polymers can be combined with drugs affording a slow release hydrogel system upon aqueous contact that would hydrolyze to readily excreted innocuous byproducts.

Thank you for reading these proposals.

Dr. Robert B. Login

References:

1. Le Corre, Stéphanie S., et al. "Atherton–Todd reaction: mechanism, scope and applications." *Beilstein journal of organic chemistry* 10.1 (2014): 1166-1196.
2. Duda, Andrzej, et al. "Milestones in development of a ring-opening polymerization of the heterocyclic monomers-view from a personal perspective." *Polimery* 59.1 (2014): 4-19.
3. Pretula, Julia, K. KAŁUZYNSKI, and Stanislaw Penczek. "Synthesis of poly (alkylene phosphates) with nitrogen-containing bases in the side chains. I: N-and C-substituted imidazoles." *Macromolecules* 19.7 (1986): 1797-1799.
4. Klosinski, Pawel, and Stanislaw Penczek. "Synthesis of models of teichoic acids by ring-opening polymerization." *Macromolecules* 16.2 (1983): 316-320.
5. Troev, Kolio D. *Polyphosphoesters: chemistry and application*. Elsevier, 2012.
6. Troev, Kolio D. *Chemistry and application of H-phosphonates*. Elsevier, 2006.
7. V Salin, Alexey, et al. "The Pudovik reaction catalyzed by tertiary phosphines." *Current Organic Synthesis* 13.1 (2016): 132-141.