

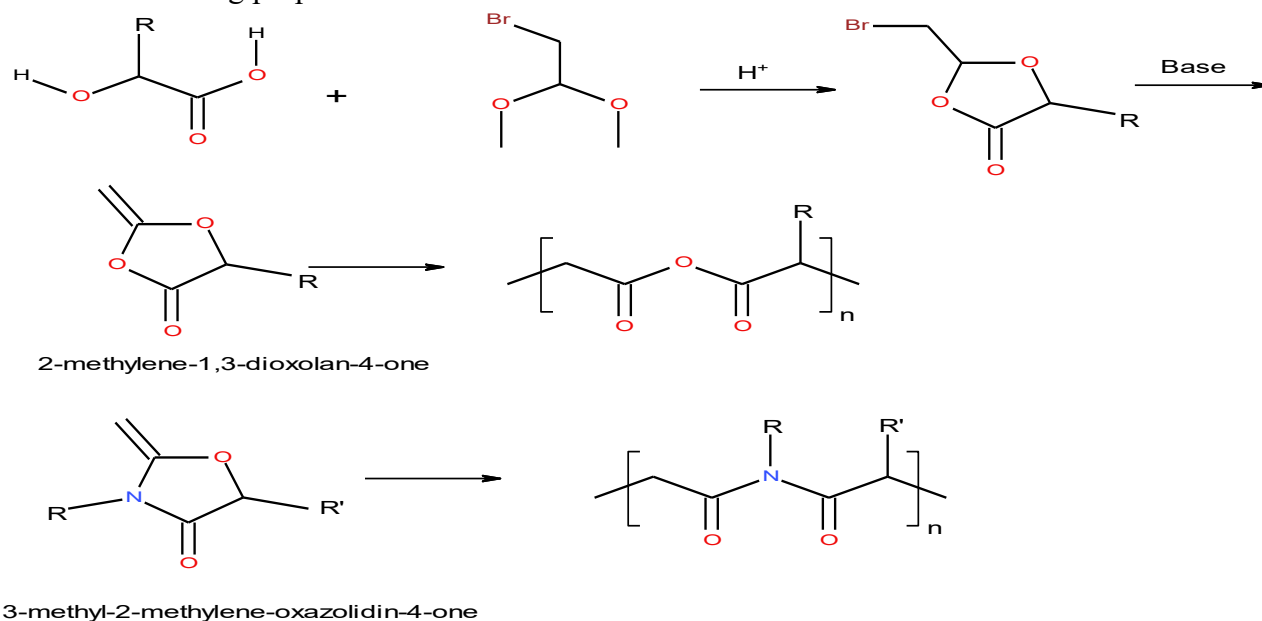
## rROP Monomers for the Synthesis of Polyanhydrides

By: Robert B. Login (rloginconsulting.com)

My previous article concerning rROP lactam monomers (see pdf on my web page) led me to think about other new monomer structures. After reading numerous rROP articles, it seemed to me that every possible structure had been discovered. A recent extensive review article that does a very good job of covering this chemistry, renewed my interest in new ideas.

Tardy, Antoine, et al. "Radical Ring-Opening Polymerization: Scope, Limitations, and Application to (Bio) Degradable Materials." *Chemical reviews*, 117.3 (2017): 1319-1406.

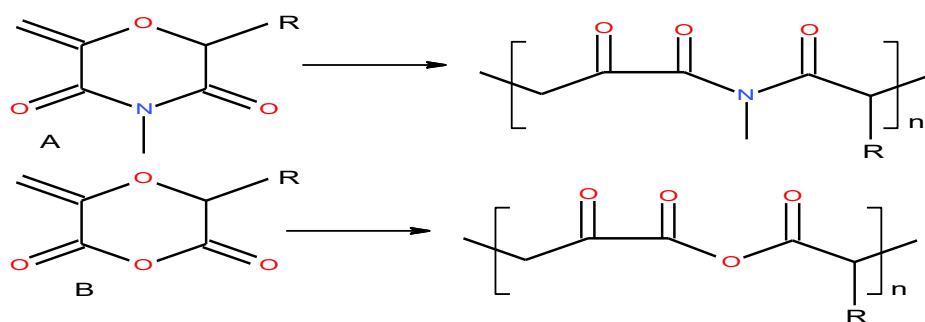
This review clearly shows that the best rROP monomers have one or two or both of the following properties; a strained ring and/or a substituent that stabilizes the forming radical. Apparently, 3, 5 and 7 are the major rings that have enough strain to open up but if the forming radical is also stabilized by those moieties that stabilize vinyl and acrylic monomers, so much the better. With this in mind, I came up with the following proposal:



Scheme 1: Conditions that will not hydrolyze the ester while forming the methylene are required. Possibly a silver salt and a mild base like a bicarbonate might work or the reaction could be conducted in a suitable non-aqueous solvent with a sterically hindered base that will not attack the ester.

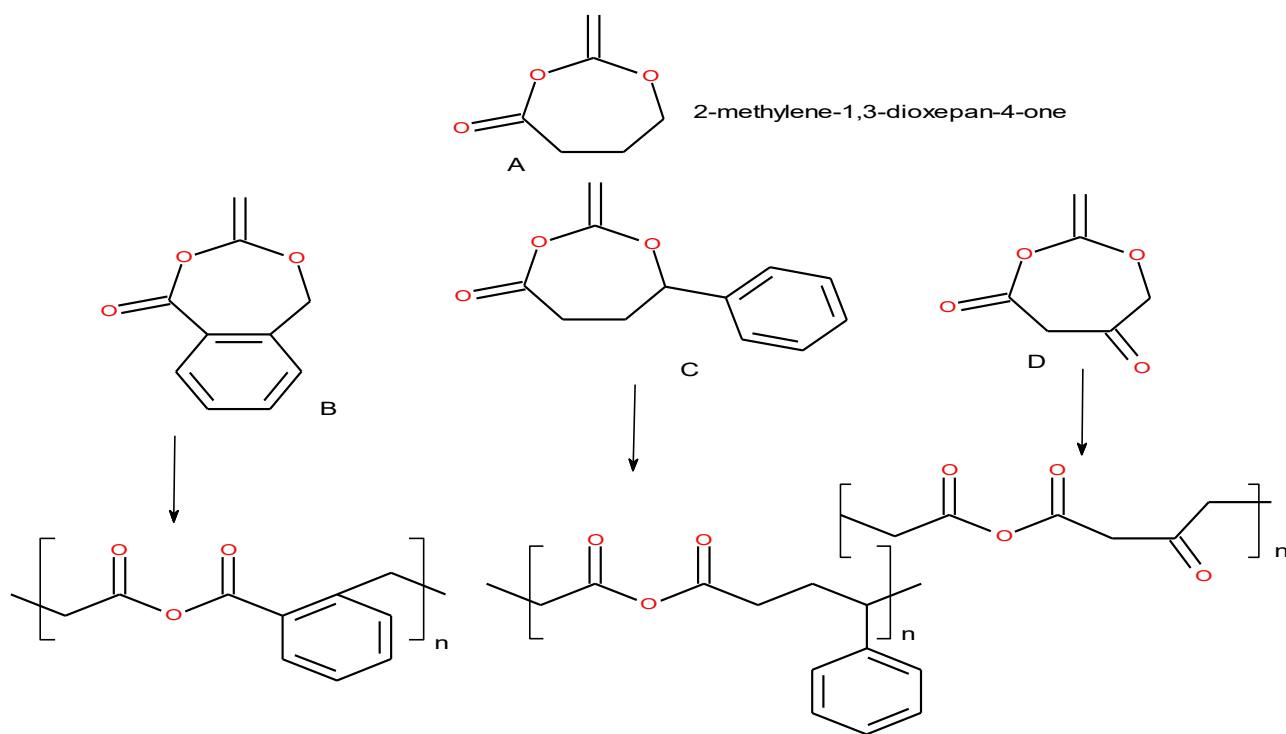
If the rROP will proceed with the amide, assuming it can be prepared, then an amide would be more resistant to ring-opening side reactions.

Searching everywhere for 2-methylene-1,3-dioxolan-4-one references, I couldn't believe that there were none. In fact both Google and Google Patents had no hits for this monomer name (when in quotes). This is in my mind very unusual because this monomer has all the requirements for rROP monomers, 5 membered ring that forms a stabilized radical alpha to the ester just like the acrylates. The R group can be another stabilizer, if that's needed. I see no reason why this monomer would not polymerize by the rROP mechanism to generate backbone anhydrides by a free radical mechanism.

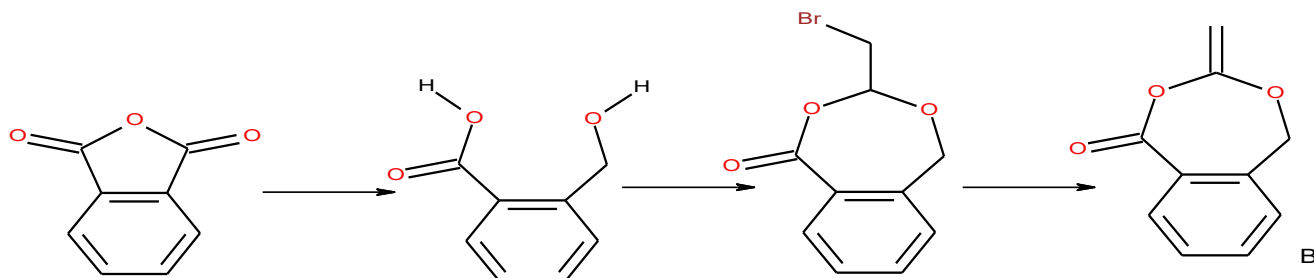


Scheme 2: Imide A might be easier to synthesize because it would be more hydrolysis resistant.

Scheme 2 illustrates another approach to anhydride and imide backbone polymers. This idea has the advantage of the methylene is in the same position as in the acrylates and the ring open initial radical is also in a acrylate motif.



Scheme 3

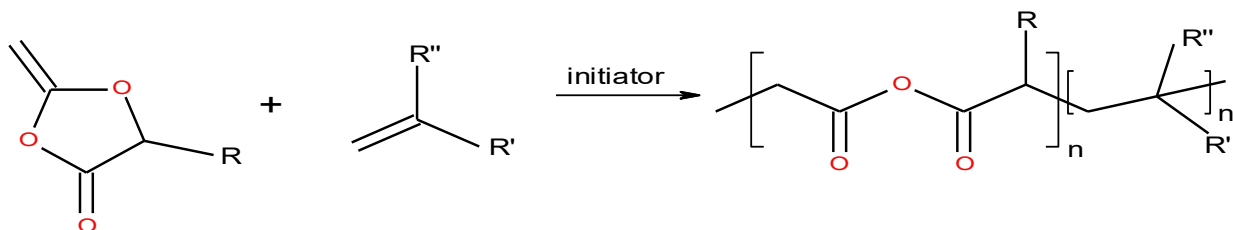


Scheme 4

Seven membered cyclics can also be described as in scheme 3. Scheme 4 shows how

monomer B can be prepared from commodity RM's such as phthalic anhydride( conditions to prevent hydrolysis of the ester would have to be devised).

All of said monomers could be copolymerized with a variety of free radical polymerizable monomers such as ethylene, acrylates, vinyl esters, NVP, styrene etc. Copolymers with acrylates would result in plastics that would have high tg's and mp's with high tensile strength but that would readily degrade especially in water from the plastic surface in.



Scheme 5: Generalized copolymerization with vinyl monomers.

Monomer B (scheme 4) could generate a polymer that would also form a degradable plastic. Such plastics can function in the many applications like those proposed for polyanhydrides. In fact monomer B can be prepared from commodity RM's such as phthalic anhydride.

Polyanhydrides are a very big deal. Numerous references indicate the intense interest in them especially for a variety of medical applications.

"The basic types are investigated for drug delivery, whereas modified versions are useful in orthopedic applications and tissue engineering. The most extensively investigated polyanhydride is poly [(carboxy phenoxy) propane-sebacic acid] (PCPP-SA). Gliadel® is based on PCPP-SA which is used as a delivery matrix for controlled delivery of the chemotherapeutic carmustine to treat brain cancer. Septacin®, a copolymer based on 1:1 sebacic acid and erucic acid dimer, is used for the delivery of gentamicin in the treatment of osteomyelitis. Poly (anhydrides-co-imides) have been developed in order to combine the mechanical properties of polyimides with surface eroding properties of poly anhydrides, and they are being explored as scaffolds for tissue engineering."

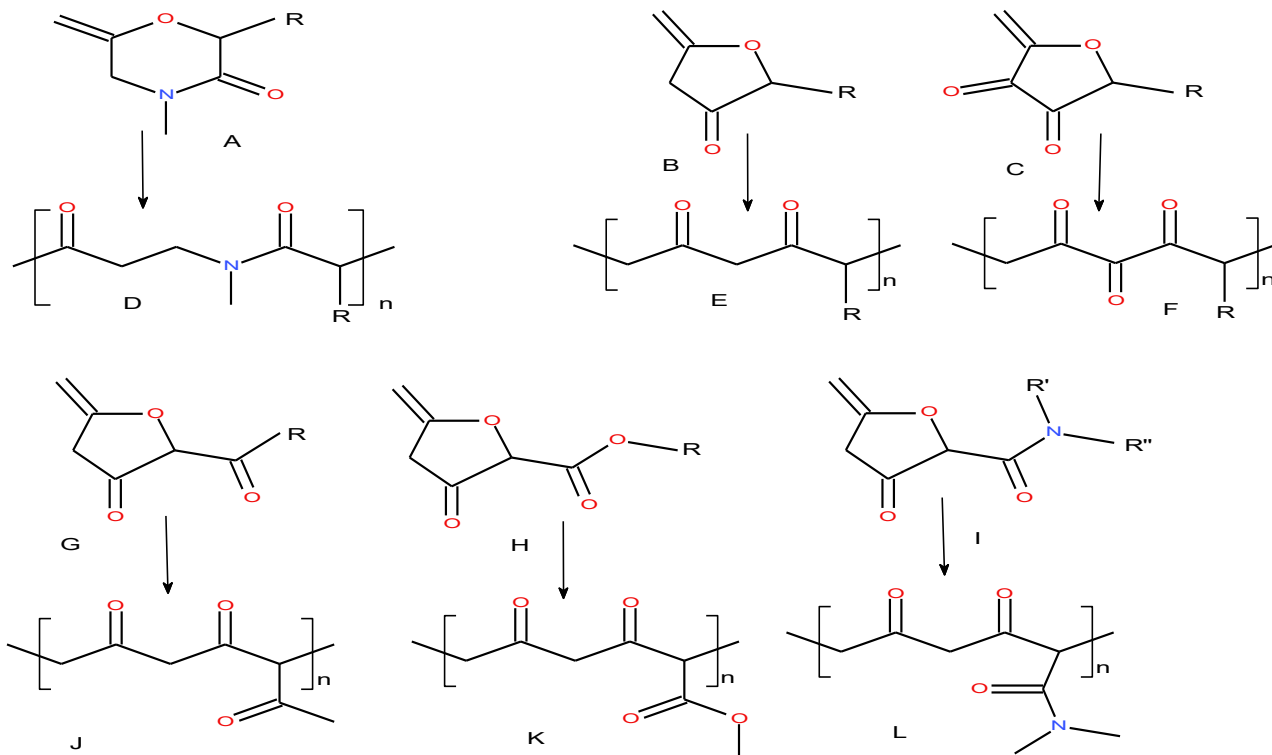
Doppalapudi, Sindhu, et al. "Biodegradable polymers—an overview." *Polymers for Advanced Technologies*; 25.5 (2014): 427-435.

Several very recent books concerning polymers for medical applications have chapters devoted to polyanhydrides. Therefore, I'm concerned that I have not found any literature concerning my proposals?

Perale, Giuseppe, and Jöns Hilborn, eds. "*Bioresorbable Polymers for Biomedical Applications*"; *From Fundamentals to Translational Medicine*. Woodhead Publishing, 2016.

Zhang, Xiang Cheng, ed. "*Science and Principles of Biodegradable and Bioresorbable Medical Polymers: Materials and Properties*." Woodhead Publishing, 2016.

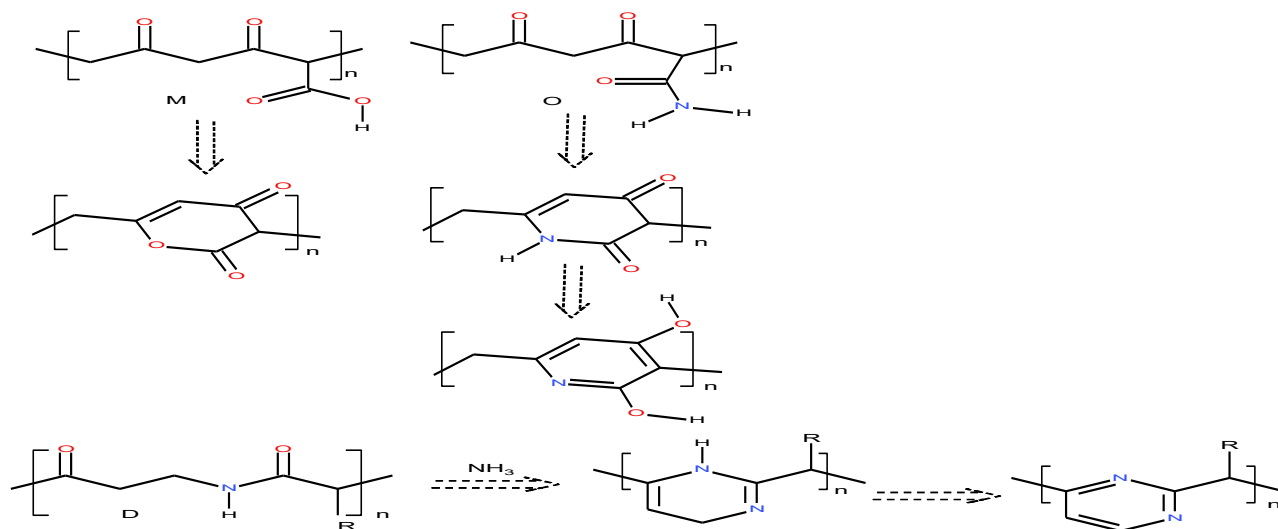
Additional ideas:



Scheme 6 (note D has an extra methylene by mistake)

Scheme 6 furthers the idea that as long as the propagating initial radical is stabilized then these proposed monomers would undergo rROP polymerization. Obviously the way to prove this would be to synthesize said monomers.

Scheme 6 shows some very interesting polymers with ketone and polyketone functionality. They would probably absorb in the uv or visual. They would be able to form many unique derivatives based on ketone chemistry especially a variety of heterocycles in the polymer backbone.



Scheme 7:

Scheme 7 doesn't take into account reactions with the carbonyls from two adjacent repeat groups and for example, amines. However, it is obvious that the proposed polymers can react further to afford backbone heterocycles and other valuable derivatives.

Thank you for reading these proposals!

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