Pyrrolidone analog based Polymers

By: Robert B. Login

Vinyl Monomer based Macrocycles

I retired in 1996 after eleven years heading up GAF/ISP's polymer science R&D. After this time, interest in living free radical polymerization intensified. I knew little of this revolution in free radical polymerization at the time but I have admired this blossoming technology ever since. Now, with its use, one can control the polydispersity, end-group structures, morphology and MW of free radical polymerization. The overall name given this is CRP or controlled radical polymerization.

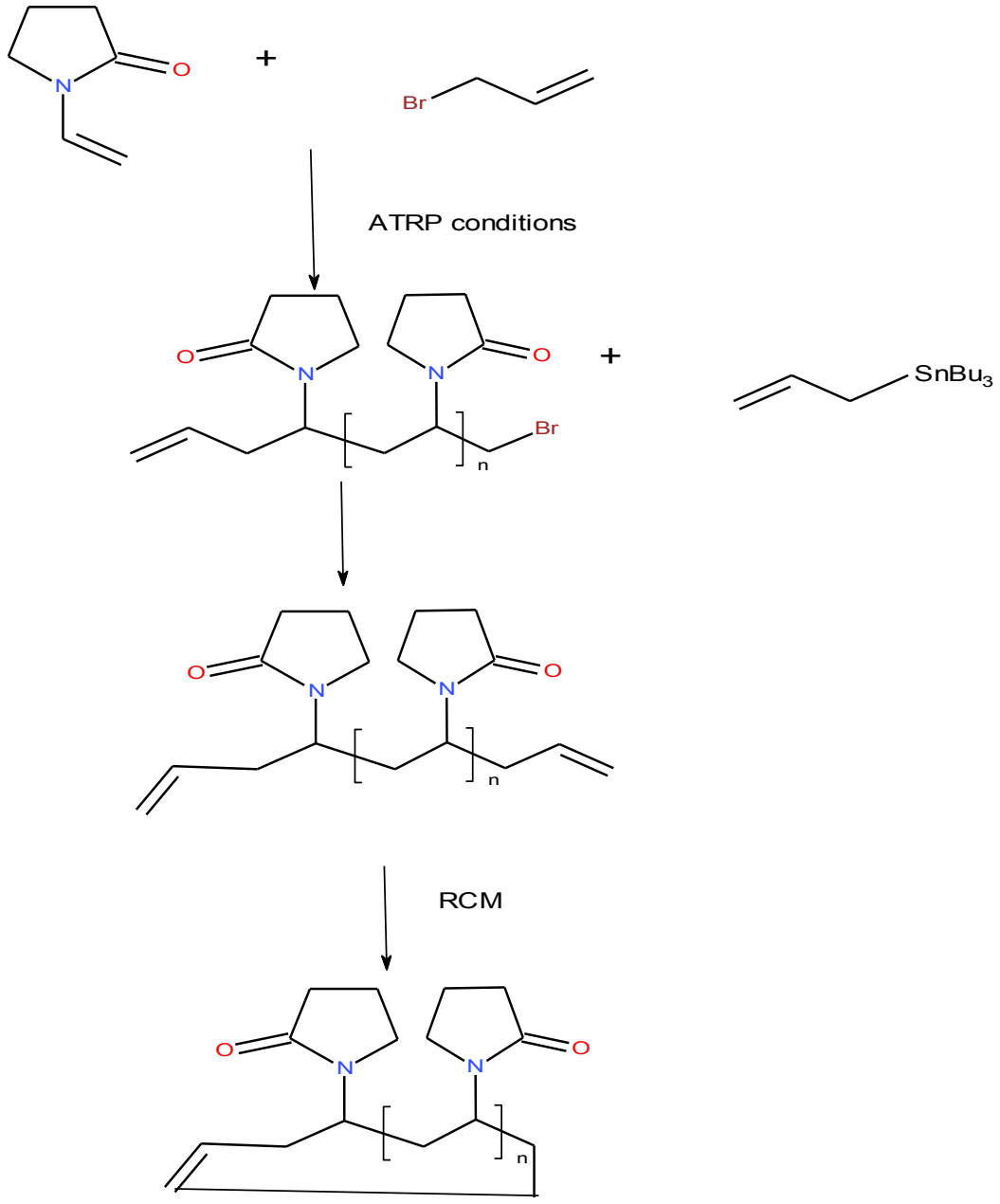
Before CRP, MW was determined by the amount of initiator and the concentration of monomer(s). The end groups were determined by the nature of the initiator and or the solvent employed. AiBN analogs with selected functional groups could be employed to initiate polymerization which would attach the functional group to the polymer. A solvent with a labile proton could be employed to exchange with the initiator to then initiate polymerization. The other end of the polymer was more problematic. It was determined that termination could occur by combination or disproportionation or abstraction of a labile proton. Obviously all of this resulted in polymers with a variety of end structures and high polydispersity, usually greater than 1.5 and usually 2-4.

CRP allows the polymer scientist to completely control the mw, polydispersity and end group structure. Not only those parameters, but many structures not possible by classic FR polymerization such as true block or poly block polymers by adding monomers sequentially, and allowing new morphologies such as comb, brush and star configurations. This is all made possible by the “living” nature of CRP. In this case, the radical end of the growing polymer is in equilibrium with a capping molecule that will still allow FR polymerization but in a very controlled way. Whenever this capping compound reversibly reveals the FR, a monomer can add to the chain end before the cap reestablishes itself. This is comparable to the “living” ionic polymerizations that predated, CRP.

There are many reviews of CRP that will afford a much more detailed accounting of this technology for those interested individuals.

CRP has been employed to prepare macrocycles. One method was to use “Click” chemistry in which an acetylene group is at one end of the polymer and an azide group at the other end. Under the correct conditions of catalyst, dilution, temperature and time, high yield cyclization is possible. Cyclization can also be achieved by Ring Closure metathesis(RCM) or by the McMurry reaction of terminal cabonyls.

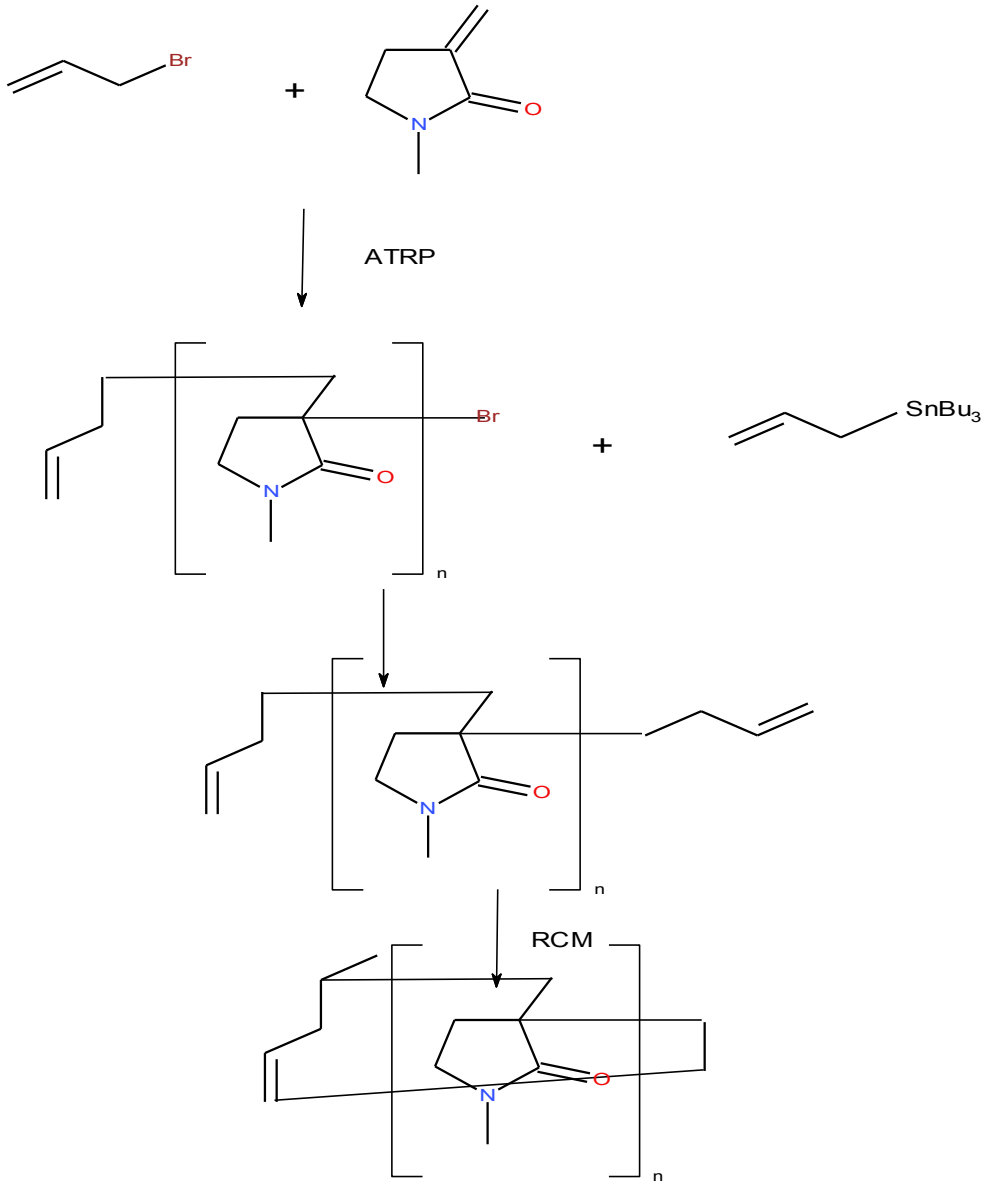
ATRP(atom transfer radical polymerization) is a very useful technique to prepare terminally functionalized polymers from a variety of FR polymerizable monomers. Using ATRP to fix allyl groups to polymer terminals, I envisioned the following sequence:



There's one glaring problem with this idea...VP currently doesn't work well with ATRP. If it did then this would be interesting to try. The problem with VP is that it is not a resonance stabilized radical intermediate. This results in a very reactive FR that ATFR capping is hard to control with the chain transfer agent. Without this reaction to stop the

FR from propagating uncontrollably, the whole idea of ATFR is lost. Matyjaszewski and Tsarevsky in a 2014 review point to VP and VAc as monomers that will require new catalysts and techniques in order to control their polymerization(Molecular Engineering by Atom Transfer Radical Polymerization, JACS 2014, 136, 6513-6533).

Why would anybody bother with cyclic PVP? Cyclic polymers are superior because they have no end groups. This results in higher TG, reduced hydrodynamic volume. This also results in lower melt/solution viscosity, higher melt densities, lower shear viscosity, amongst others(Quirk et. al., Macromolecules, 2011, 44, 7538-7545.) Such differences would afford “PVP's” that did the job at lower concentrations, or were superior film formers, tablet binders, hair fixatives and so forth.
I would propose another way around the current ATRP situation with VP as illustrated in the following scheme:



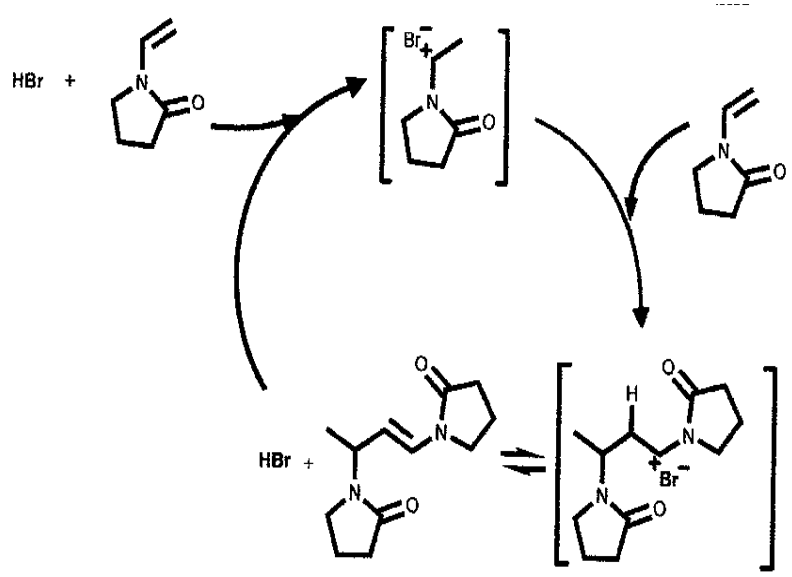
Adachi et. al. Macromolecules 2008, 41, 7898-7903.

3-methylene-N-alkylpyrrolidones(MNAP) are known monomers that are readily FR polymerized and are of the resonance stabilized FR monomers that work so well with ATRP. Because ATFR allows one to synthesize oligomers of controlled size, a variety of ring can be prepared by RCM. Furthermore, copolymers with suitable monomers can be easily prepared. If you study the ATFR literature, you will see the vast variety of structures other than macrocyclics are possible with this ingenious technique. MNAPS have a literature; for example, Iskander et. al., Macromol. Chem. Phys., 197: 3123-3133; 1996. Also Schmitz et. al. USP 4,522,997 and Song et. al., USP 5,035,884 and many more. There use in Macrocycles would be novel and new. The pyrrolidone groups would point out of the ring affording a cavity of significant complexing ability. These macrocycles would also be water soluble.

The problem with MNAP chemistry would be to work out a scalable synthesis. I point out that if Reppe was alive today, he would be laughed at suggesting his route to VP! These water soluble polymers were found to work as a blood expander, so he was supported. In fact the US stockpiled PVP in air raid shelters encase of an atomic attack. Not until it was found that PVP was hard to eliminate from the body was its use as a blood expander abandoned(note it appears that this problem is MW related. I have suggested alternatives to PVP in several of my reports if interested. Macrocyclics of MNAP might fill this application and be easily excreted.

Acid Catalyzed:

NVP (N-vinyl pyrrolidone) can be readily hydrolyzed in aqueous acid to 2-pyrrolidone, and acetaldehyde; however, under anhydrous conditions, acids like HBr will dimerize NVP. This reaction can produce dimers in very high yield if not quantitatively.



Huang et. al. Macromolecules, 2009, 42(21), pp8198-8210

Madl and Spange, “ “ , 2000, 33, 5325-5335
A. Guinaudeau et. al. “ “, 2014, 47, 41-50
Such a high yield reaction would be ideal for polymerization and this is possible in the case of my previously described dimer “pyrrolidones”. Figure 1 lists some possible candidates. Figure 2 illustrates one possible dimer “pyrrolidone” polymer:

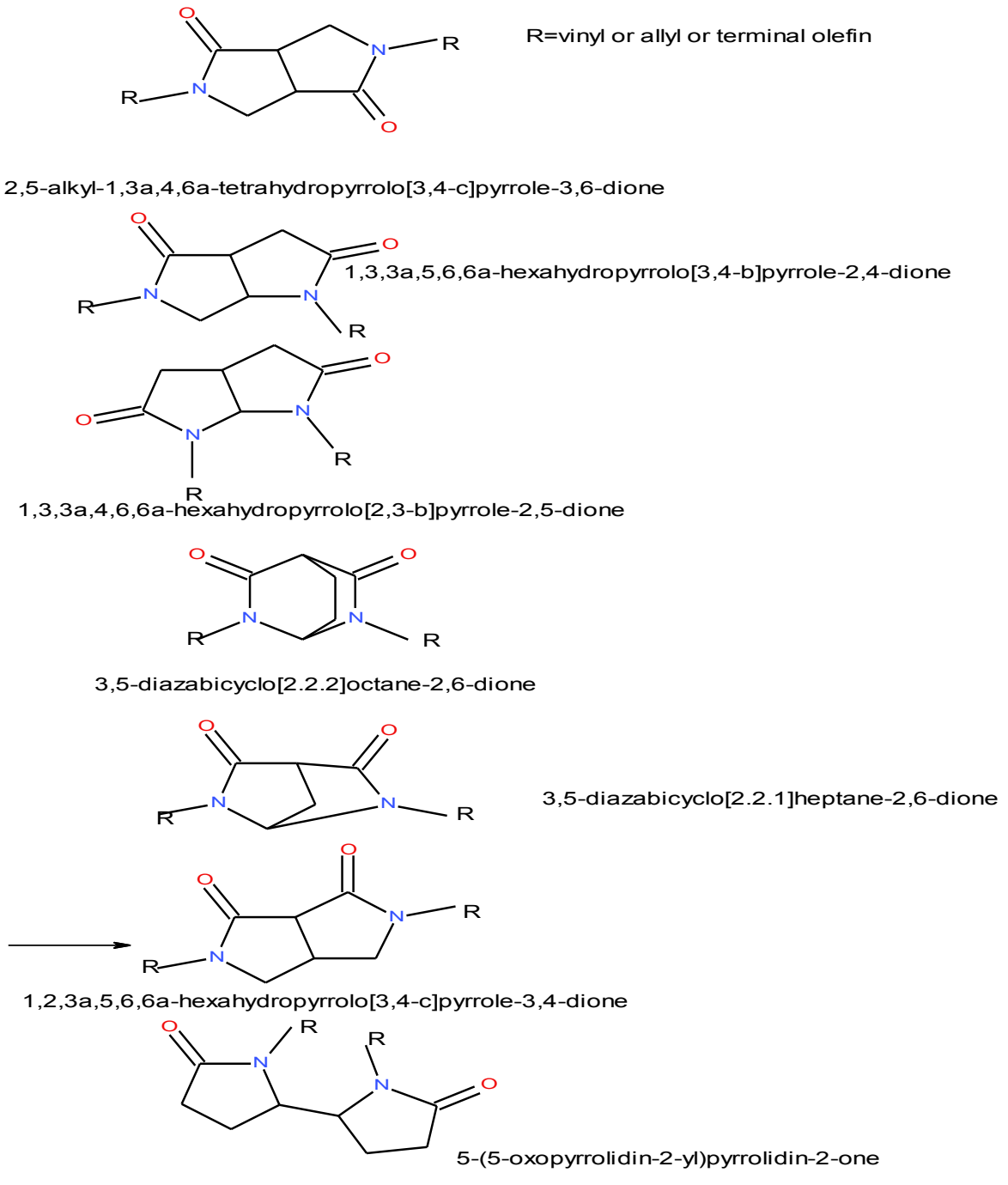


Figure 1: Some possible starting N-vinyl candidates for acid catalyzed poly-dimerization.

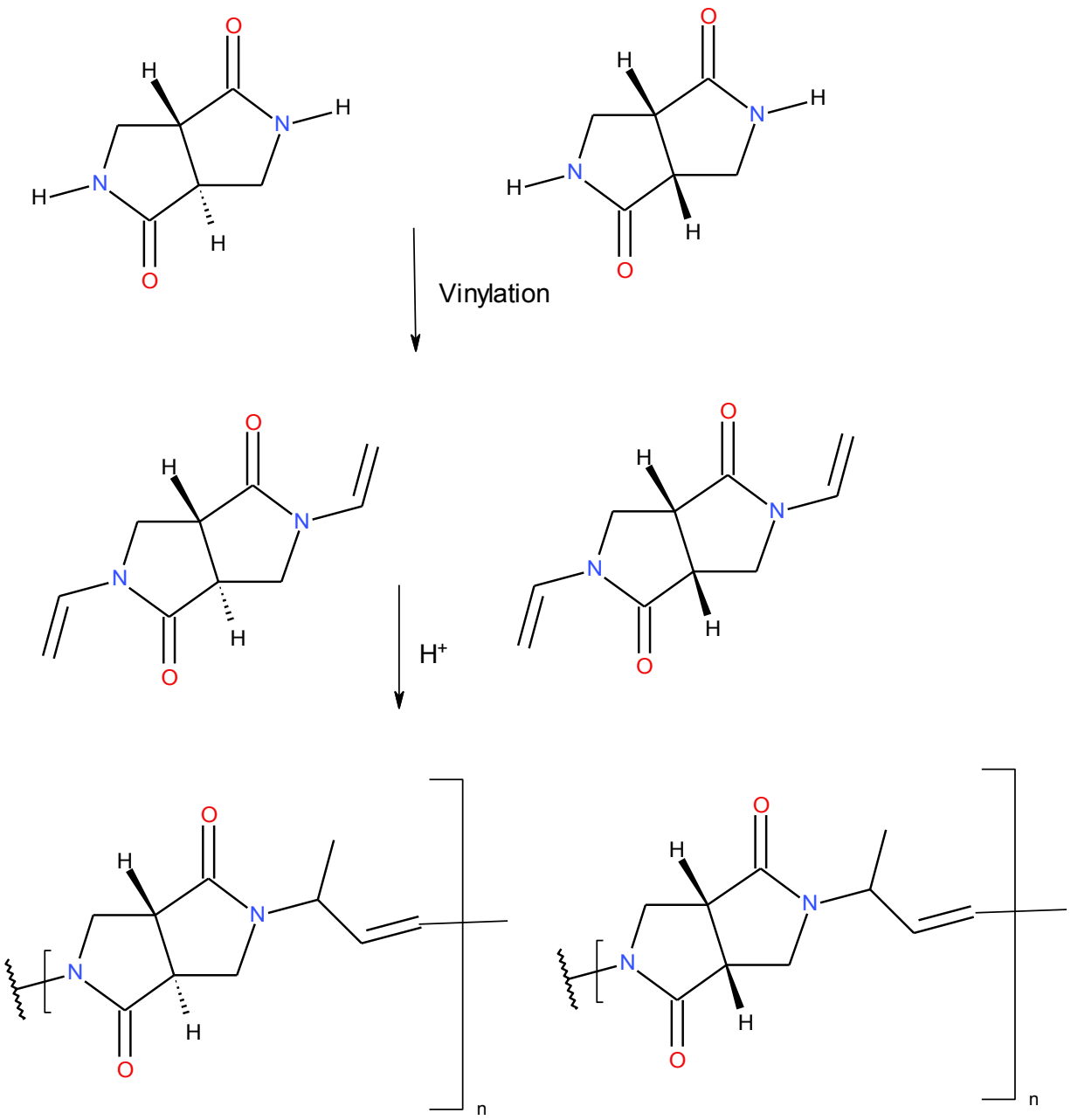


Figure 2: One possible acid catalyzed dimer N-vinyl candidate isomers.

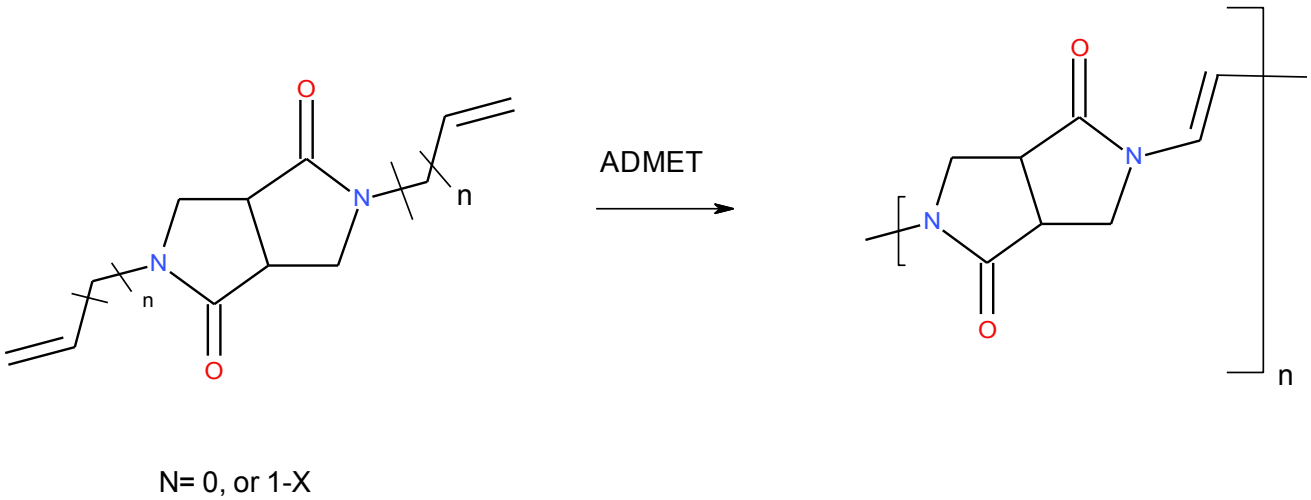
I've only showed one possible structure from the several revealed on my web page (rloginconsulting.com) which should be accessed for proposed dimer synthesis details.

When in the presence of water said polymers will hydrolyze, especially under acidic conditions. At basic pH's, this hydrolysis would be suppressed; therefore, control of the breakdown of these polymers could be controlled at will and in addition said polymers would be water soluble, another advantage. They could be put to a variety of uses such as the delivery of poorly water soluble drugs, excipients such as tablet binders and disintegrants, cosmetic and personnel care additives such as hair care

conditioners, thickeners, lubricants, mascaras and so forth. The advantage for the formulator is not only its efficacy but the potential that the product after use can be easily removed forming innocuous byproducts. Also like pyrrolidone, these dimers could exhibit low skin and eye toxicity.

ADMET:

The fact that terminal olefins are a consequence of the vinylation of these dimers also opens up the possibility of employing ADMET condensation polymerization. My search of the literature revealed nothing even similar to this idea but it seems totally reasonable to me. The problem would be to evaluate the current metathesis catalysts for proper activity. ADMET has been used to polymerize dienes containing amide functionality(P. Atallah et. al.[Wegners group], Macromolecules, 2013, 46, 4735-4741.) and p.436 in Nontraditional Step-Growth Polymerization: ADMET (Synthetic Methods in Step-Growth Polymers, 2003, Wiley). Therefore, it sould work with "pyrrolidone" lactams.



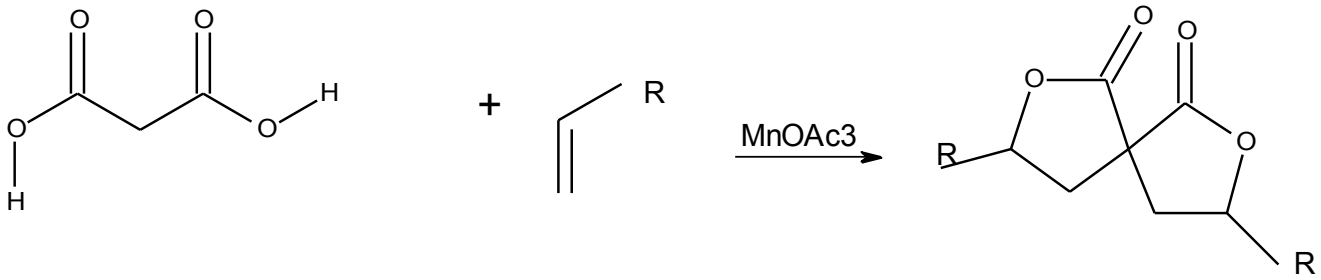
N= 0, or 1-X

Figure 3: One example from figure 1 illustrating ADMET polymerization.

Some of the Dimer "Pyrrolidones" shown in figure 1 might not polymerized with ADMET, but will undergo RCM(ring closure metastisis) especially if a low strain cyclic structure is possible. Those that would form strained or larger than seven membered rings will form polymers. ADMET will form high MW polymers of known design. Wherever PVP is employed, these ADMET polymer analogs might also be useful. Because they are unsaturated like the ones previously described prepared by acid catalysis, these will also be stable under basic pH but hydrolyze under acidic conditions. In other words, they can be converted at will into innocuous byproducts, unlike PVP. This would make them ideal as excipients for a variety of pharmaceutical applications. Hydrogenation would produce stable aqueous polymers.

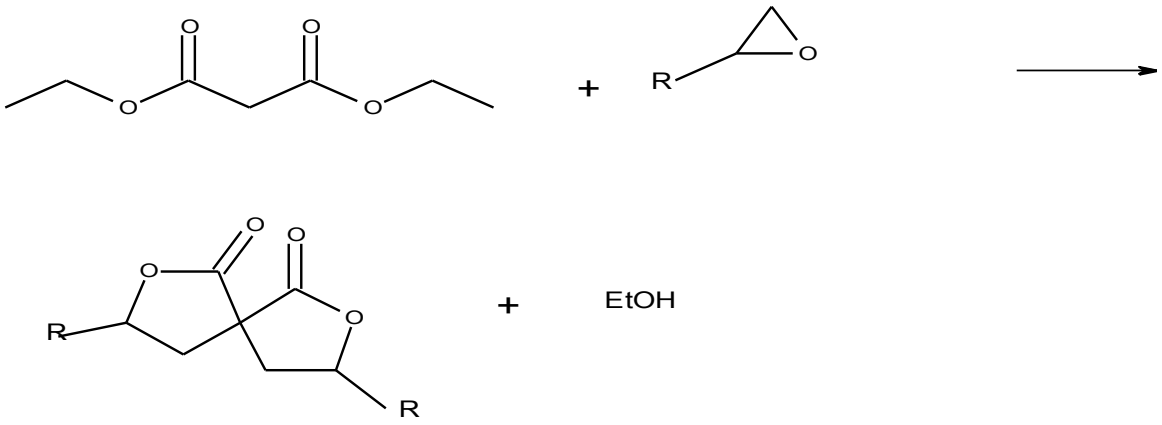
Spiropyrrolidones;
As previously described in my report: Pyrrolidone backbone polymers, it is also possible to prepare similar dimers from spiro-dilactones. They can be reacted with ammonia or amines like allylamine and so forth to prepare similar structures as above that would work with ADMET polymerization.

The most direct reaction is the unique one step high yield reaction of alkene and malonic acid in the presence of manganese(lll)acetate:



Fristad and Hershberger; JOC 1985, 50, 1026-1031
Jian-Qiang et. al. Chem J. of Chinese Universities, 2001, vol. 22, #5: 851-859.

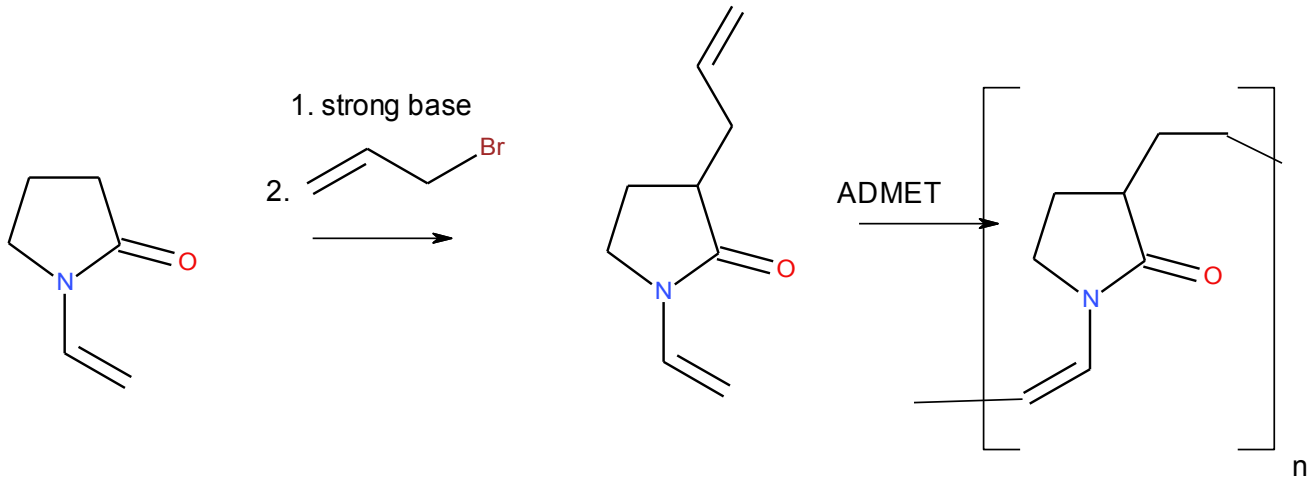
The same type of spiro-dilactones can also be prepared from epoxides by the base catalyzed reaction with a maleate:



Rebrovic and Harris; USP 4,980,342
Leuchs and Gieseler, Ber.,1912, 45, 2114
Ishido et. al. J.C.S. Perkin I; 1977, 521-530.
The above can be reacted with diallyl type amines or vinylated that would react under ADMET conditions.

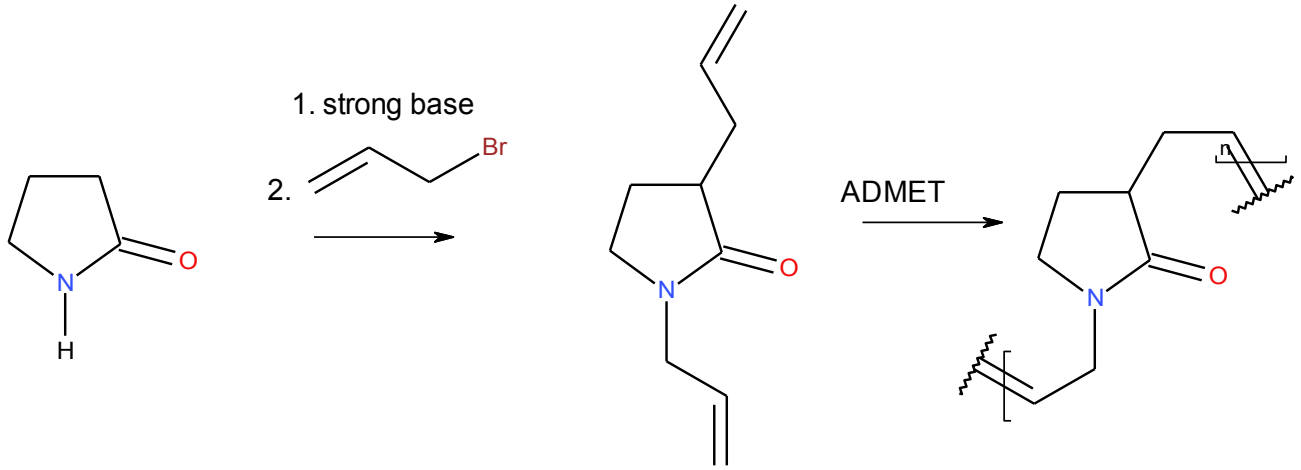
Most of the examples of terminal dienes in the ADMET literature are symmetrical but is this not a rigid requirement for successful ADMET polymerization. The following

would be another possibility.



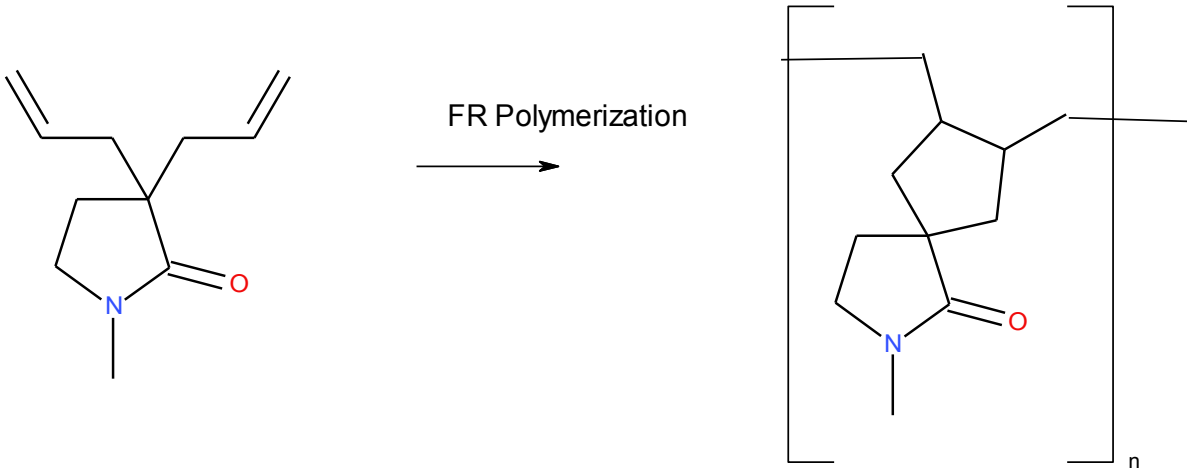
Chen et. al., Macromolecules 2010, 43, 9972-9981 claims 100% yield for the allylation of NVP.

Once again the unsaturated nature of the polymer would make it pH sensitive. If the N-allyl derivative is tried then the unsaturation would not be vulnerable to hydrolysis.



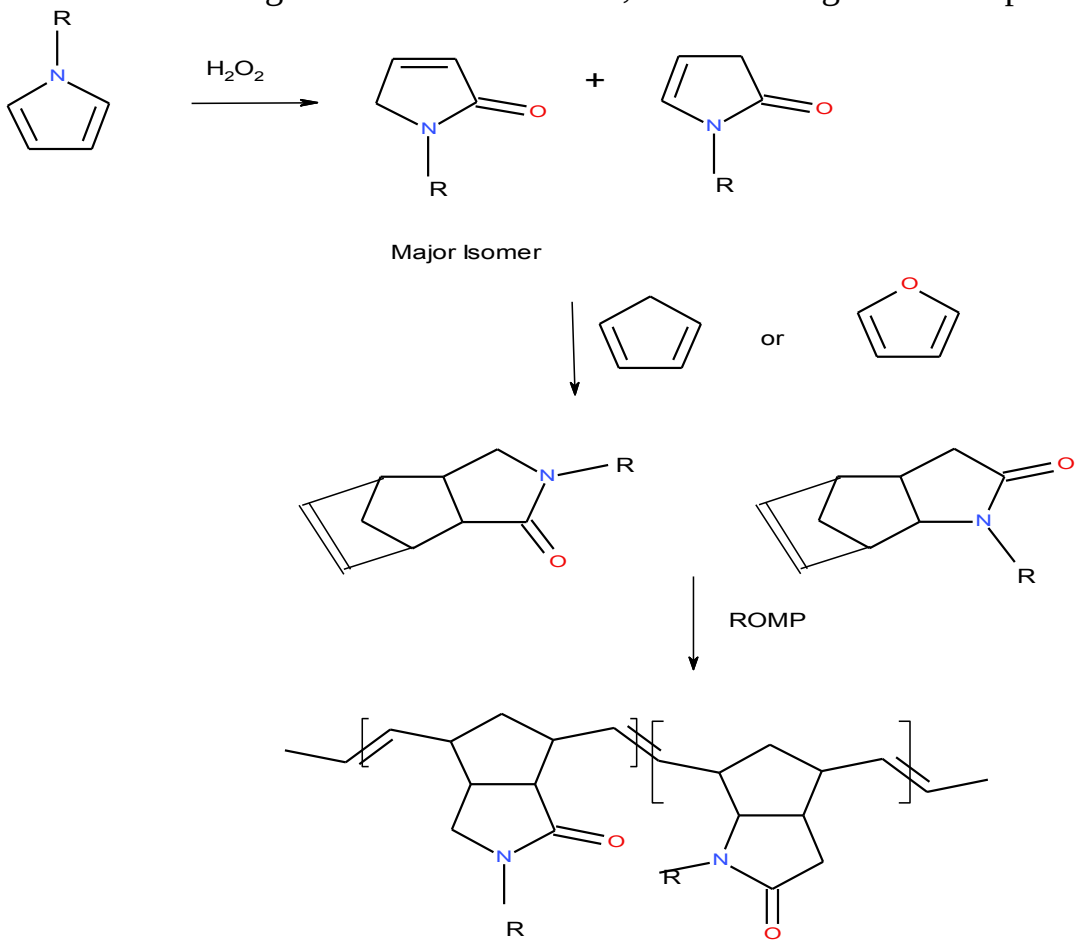
Hydrogenation of these unsaturated polymers would of course eliminate the chance of hydrolysis. Furthermore, propargyl analogs of allyl bromide will also undergo metathesis and should be considered as alternatives.

It is possible to synthesize the 3,3- diallyl of say NMP then such a monomer would readily under go FR cyclopolymerization:



Dana K. Winter et. al., J. Org. Chem. 2010, 75, 2610–2618. Synthesis of 3,3-diallyl-pyrrolidone.

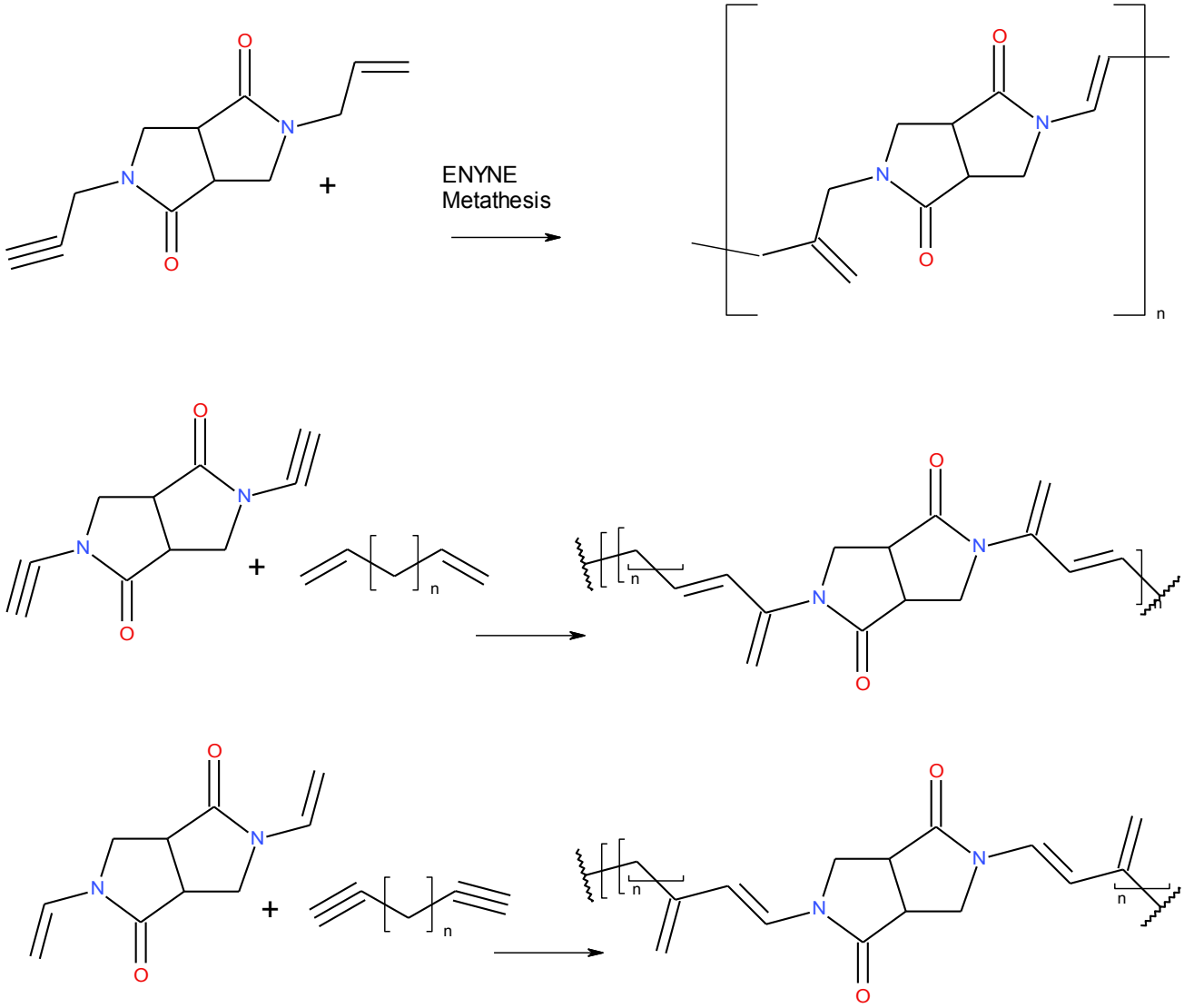
In this case, the pyrrolidones face away from the polymer backbone which has never been done and the effect of this is unknown. However, NMP is a supper solvent by which it means that it will dissolve many types of compounds and is compatible with most other solvents. This reverse structure can, I believe complex more effectively as compared to PVP. Thinking about the reverse PVP, the following scheme is possible:



See: Matson and Grubbs; Macromolecules, 2010, 43, 213-221.

This ROMP generated polymer is more hydrophobic but should also have interesting properties. This then is another method of reversing the pyrrolidone ring.

<u>Enyne Metathesis</u>:
Another possible method to generate dimer polymers is by the Enyne reaction. For example several arrangements of the ene and yne groups can be visualized:



The yne or ene groups can be separated from the lactam nitrogens by a variety of suitable spacers such as alkyl etc. For example the groups can be allylic or propargyl.

As before these unsaturated polymers can be either hydrogenated to form stable polymers or said unsaturation can be employed to hydrolyze the polymers when desired in aqueous acidic solutions.

The Metathesis chemistry is a powerful method of forming carbon-carbon bonds and its literature is enormous. This indicates the interest in this chemistry especially by academics. Industrial chemists worry about the cost and recyclable nature of the catalysts. Also since the catalysts are heavy metals, their toxicity is also an issue especially if they are difficult to remove. Recently a great deal of effort to prepare supported catalyst that work and are easy to remove is being pursued. This will allow flow-type reactors to be viable. (See, “Olefin Metathesis, theory and practice” by K. Grela; Wiley, 2014). This is what I would be working on if I was back in R&D.

I would be delighted to discuss these ideas with anyone who might be interested.

Thank You,
Dr. Robert B. Login
rloginconsulting.com