

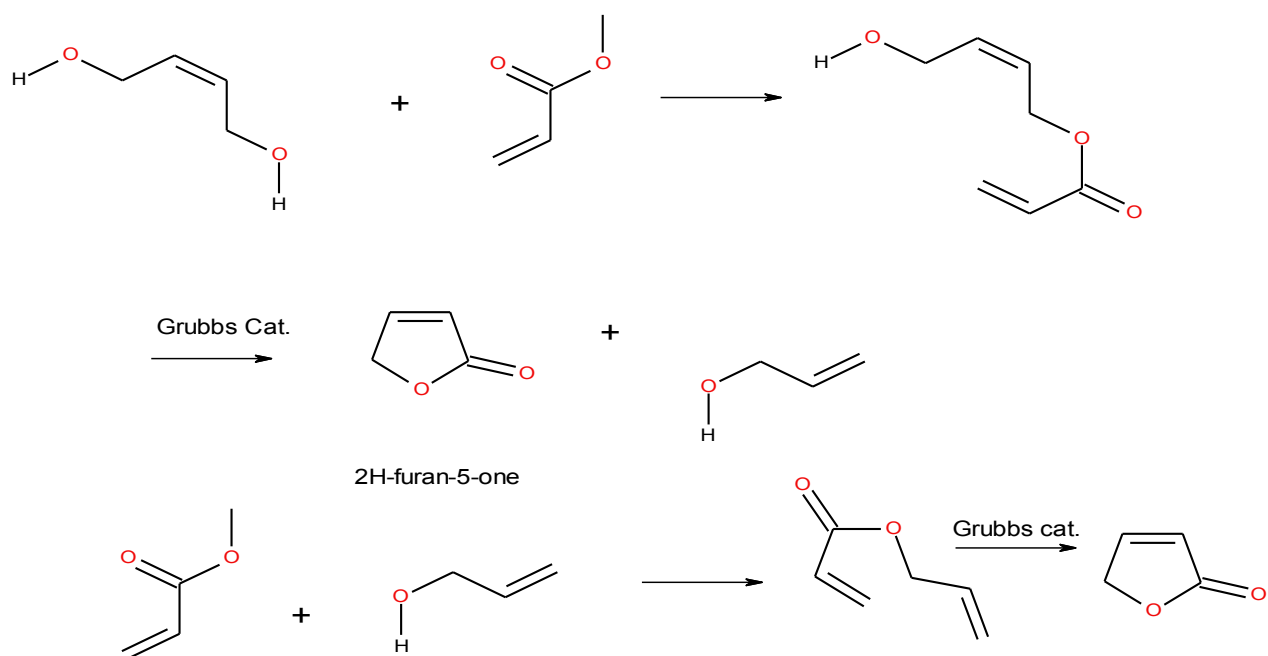
Metathesis and Polyfuranones, Polylactams and dendrimers

By Robert B. Login

Metathesis is now closing in on more than three decades of spectacular development and some of the problems with metathesis are being resolved. Recently patents have appeared claiming supported catalysts that are easy to remove and could be re-used even in flow reactors. Hence, the problem of heavy metal contamination can be eliminated. (USP 6,921,735 and 7,632,772 for example). Economics are a chief concern but new more robust catalyst continue to be developed that are much more cost effective.

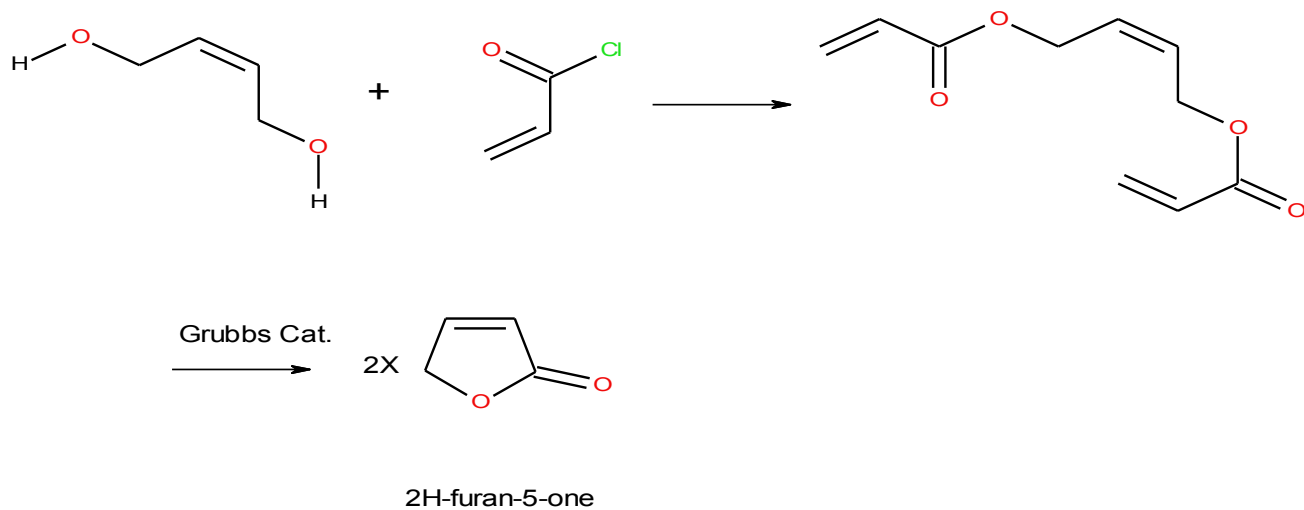
I find metathesis chemistry fascinating. When one thinks about the scope of these reactions, that double or triple bonds can be readily manipulated by RCM, ROMP, RCEYM, ADMET, CM, ene-yne etc techniques. If you are unfamiliar with these acronyms, there are many good reviews, for example the recently published, "Olefin Metathesis theory and practice", by Karol Grela ed. Wiley, 2014.

My background as the Director of Polymer Science for ISP leads me to think of acetylenic chemistry practiced by that company and how to find new and useful products based on it. I therefore began to think about 1,4-dihydroxy-2-butene an intermediate in the preparation of 1,4-butanediol, BLO, and VP. Because it has a double bond it should react with metathesis catalysts like Grubbs 2 or others and undergo Ring Closure Metathesis (RCM). Therefore I think the following scheme would be very interesting:



Scheme 1A

In this scheme, nothing is wasted, producing two moles of the expensive 2(5H)-furanones and ethylene. The diester acrylate might give two furanones directly.



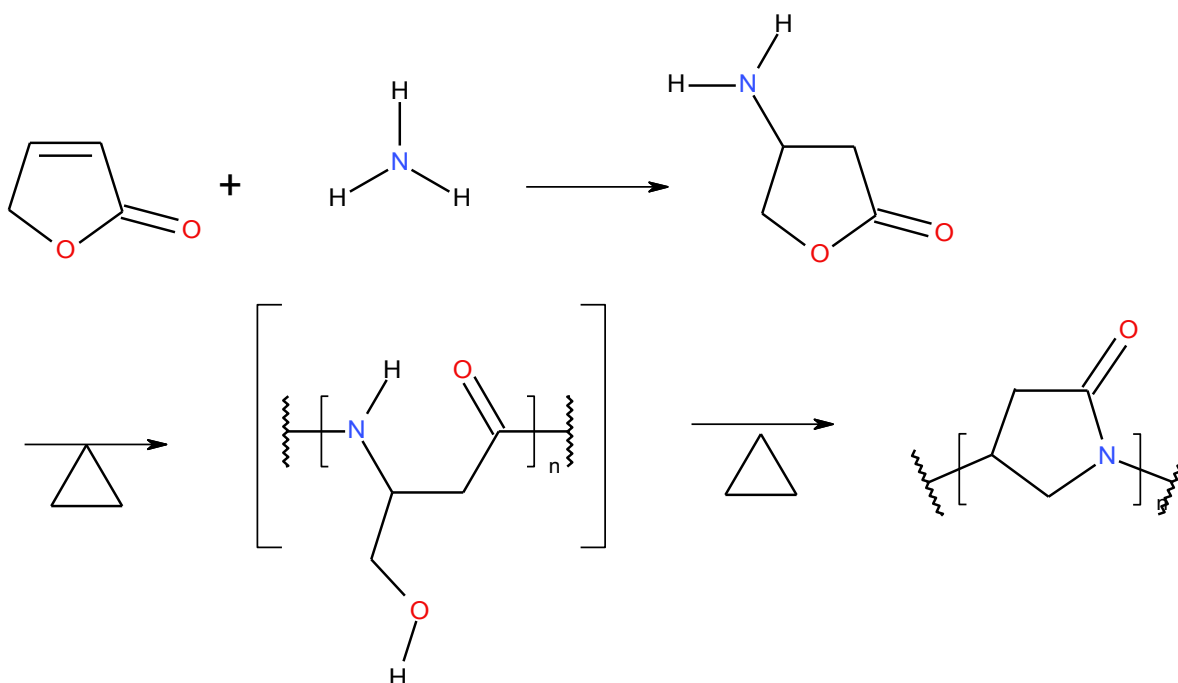
Bull. Korean Chem. Soc. 2011, Vol. 32, No. 8 3167.
 The new journal for organic synthesis, V28, Issue 2, 1996.
 Org. Lett. 2005, 7(9), pp1805-1808.
 Scheme 1B

2(5H)-furanone can be synthesized from the allyl alcohol acrylate ester, as shown above, by RCM(Org. Lett. 2005, 7(9), pp1805. And allyl alcohol can be prepared by the hydrogenation of propargyl alcohol. Whichever of the above approaches, is easier or less expensive or both, should be considered.

I have copied some of the introduction to an article; Tetrahedron 65 (2009) 5251-5256 that illustrates the interest in this compound.

"Furan-2(5H)-ones have attracted the attention of several organic chemists as valuable targets due to their presence as a subunit in many natural products isolated from a variety of sources like sponges, algae, animals, plants and insects. According to the literature reports this subunit is present in as many as more than 13,000 natural products. This core unit is the key structure to induce a wide range of biological activities like antimicrobial, anti-fungal, anti-inflammatory, anticancer and anti-viral etc. The Butenolide synthon is the core structural unit found in many bioactive natural products such as sarcophineland rubrolide, which is isolated from the colonial tunicate Ritterella rubra, as well as in synthetic drug benfurodil hemisuccinate (Eucilat)."

2(5H)-furanone (aka butanolide) is an excellent Michael receptor and will react with ammonia or an ammonia surrogates to form a new monomer. Scheme 2 illustrates this reaction.



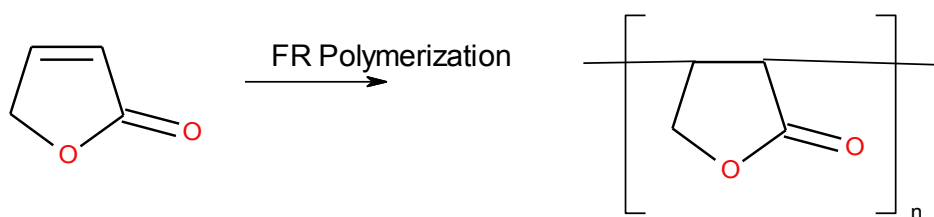
Scheme 2

The last step of this scheme is new as far as I can tell; however, several patents have issued concerning the addition of primary amines to this unsaturated lactone affording the hydroxy containing polyamides (UNSATURATED SIDE CHAIN POLYAMIDE Polymers by R. Hollingworth and G Wang, USP 6,541,601 B1; Zhi H_ Huang, et. al., US 6,399,714 B1; Rawle I. Hollingsworth, usp 6,153,724). These patents do not show how to further react the hydroxy group with the amide groups to generate pyrrolidones

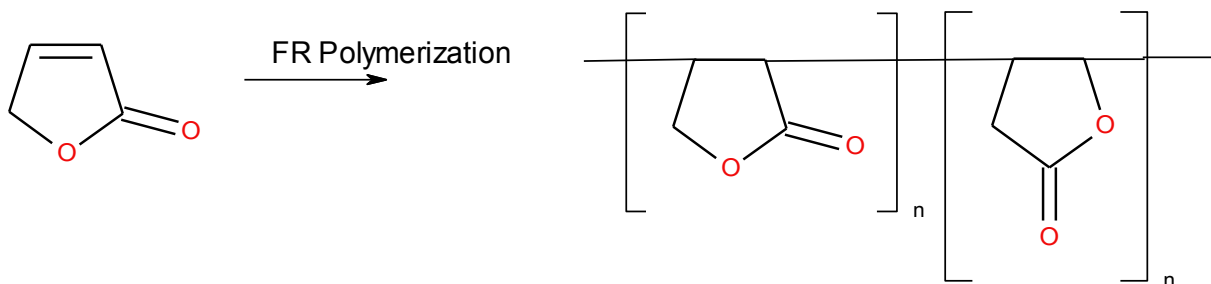
The polylactams resulting from this chemistry would be analogous to the nylon family with the added benefit of water solubility. If the MW is in the nylon range, I would predict a tough polymer possibly even a fiber former that could be handled as an aqueous solution.

Potential uses for these polyamides would revolve around their water solubility. Temporary medical applications such as sutures, erode-able implants, cell scaffolds, bandages, drug delivery etc. Such uses would be very valuable.

Free Radical Polymerization:

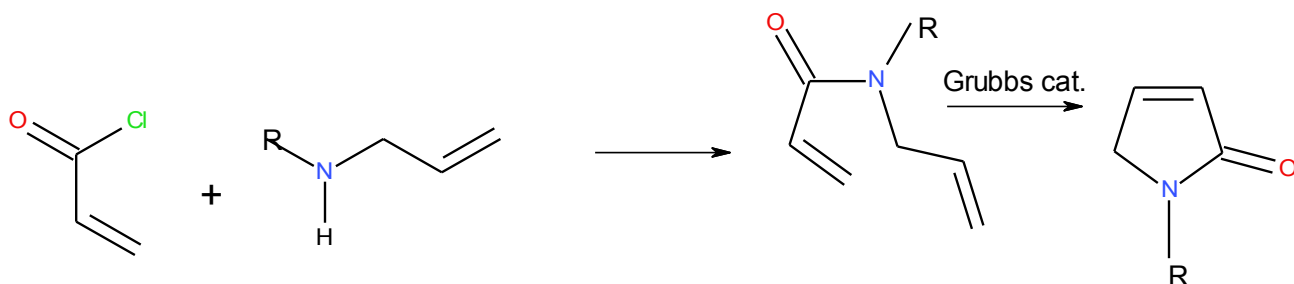


Yoon et al. USP 7,241,552 B2 Jul. 10, 2007 illustrates the FR polymerization of the 2(5H)-furanones. In this case they used angelic lactone and they claim that the lactone can polymerize in two ways:



Not only can the 2(5H)-furanones readily polymerize they can copolymerized with a variety of FR monomers. Once this polymer is available, it can be post reacted with primary amines to form hydroxy and amide pendant groups. These poly lactones can have a variety of uses but they could also further react to form pyrrolidone groups. This would be another analog to the one above (scheme 2) and the resulting polymers would have similar uses.

Acrylamide derivatives:



N-alkyl-2H-pyrrol-5-one

Bull. Korean Chem. Soc. 2011, Vol. 32, No. 8 3167

In much the same way as acrylic esters, N-unsaturated acrylamides will also undergo RCM to form 2H-pyrrol-5-ones.

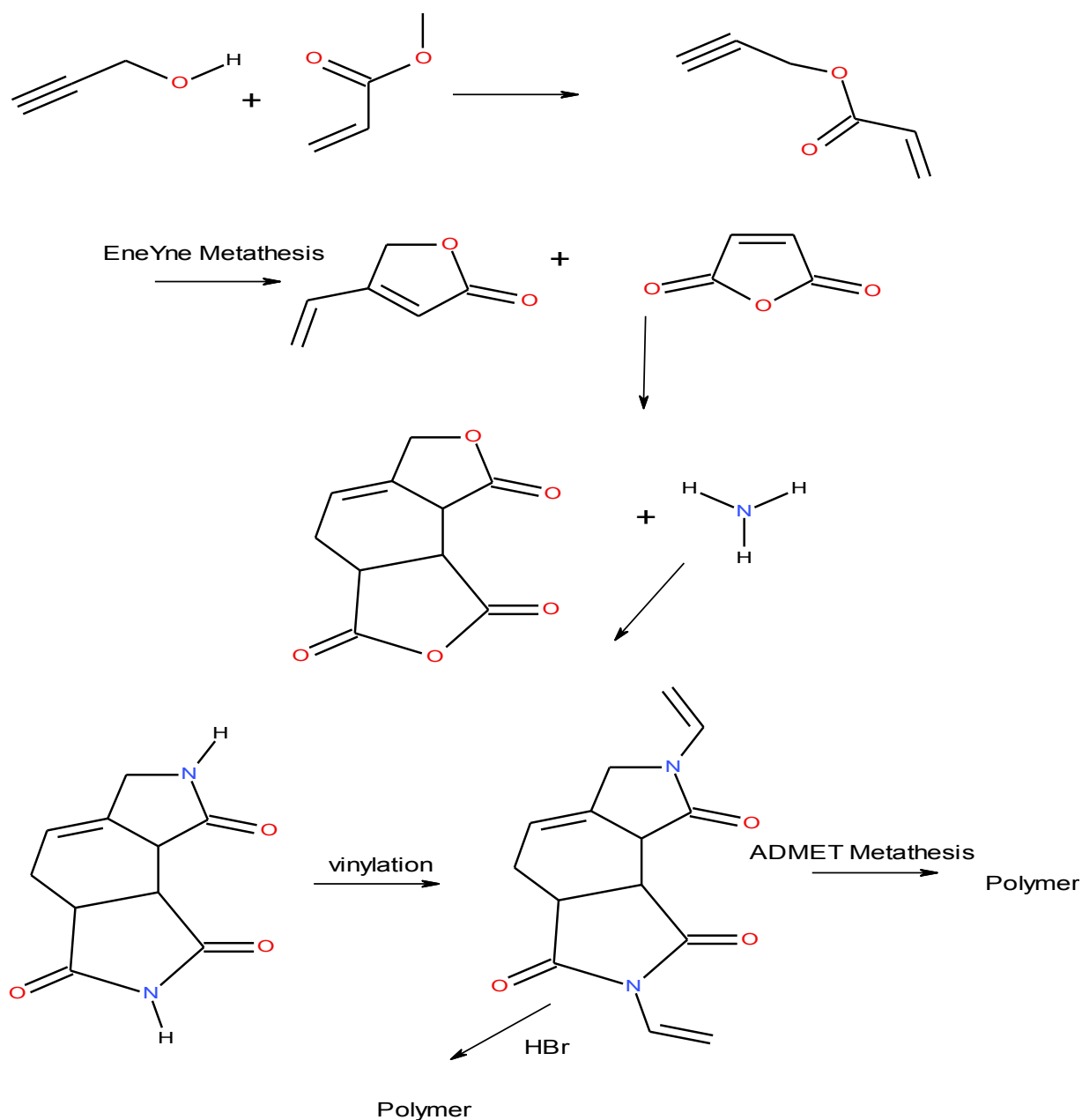
Presumably, 2H-pyrrol-5-ones will polymerize by a FR mechanism? I have not found any reference to the

polymerization of this monomer? It is possible that the reason is that the actual structure of this monomer is the hydroxypyrrol which does not polymerize? However, if it did polymerize, Said polymers would contain pendant pyrrolidone groups with the lactams pointing out away from the backbone. Such polypyrrolidones would have unique properties; for example, water solubility, complexation, iodophors, hair fixatives, tablet binders, excipients, solublizers of water insoluble drugs and so forth. In short , every job that PVP does might be done better by this polymer. 2H-pyrrol-5-one might also copolymerize with a variety of monomers. In fact this monomer would be compatible with ATRP and other living FR polymerization techniques. Should the unreactivity be true then the poly(2(5H)-furanone) post reaction route would afford similar polymers by post reaction with amines followed by condensation to pendant pyrrolidone.

It would be very nice if 2H-pyrrol-5-one's would polymerize as a plethora of interesting uses can be visualized. However the lack of references makes me think this is not the case. I would appreciate being informed if anyone knows references that would shed light on this chemistry.

Ene-Yne Metathesis:

Since propargyl derivatives are available from acetylenic chemistry, the following could be considered:



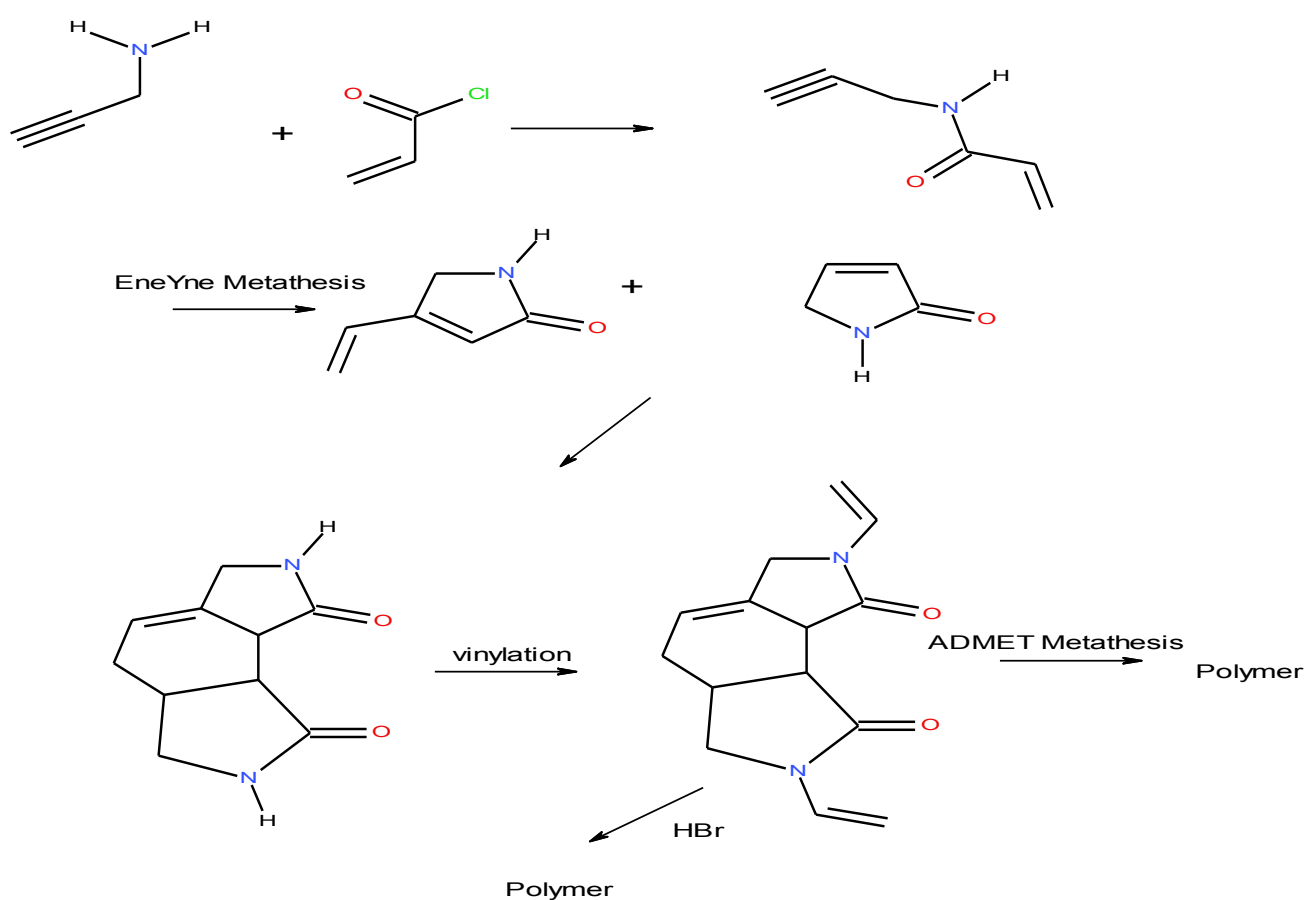
Scheme 3

The 4-vinyl derivative will undergo the Diels-Alder reaction which as I show can lead to another set of polymers. The Diels-Alder reaction can be performed along with metathesis in-situ or as a post reaction. Other dimer types have been discussed in previous reports available on my web site (rloginconsulting.com)

The ester of propargyl acid and allyl alcohol, the reverse of what's shown above, will also react by the Ene-Yne

mechanism. Obviously other unsaturated primary amines such as allylamines can also condense with these anhydride and lactone groups and undergo ADMET polymerization.

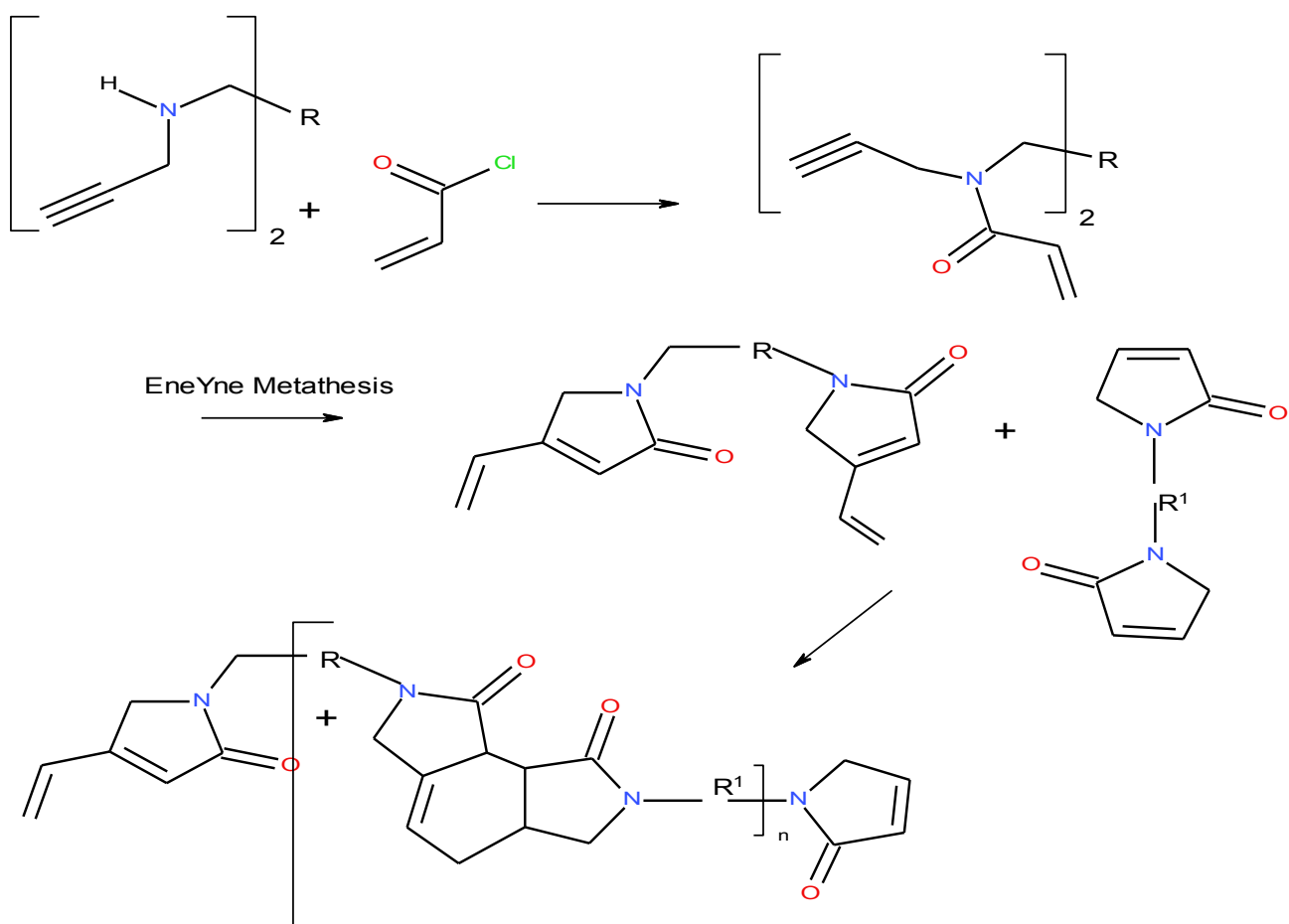
The same set of reactions are feasible with 2H-pyrrol-5-ones replacing maleic anhydride and might require fewer steps. The point is that dimer type pyrrolidone vinyl derivative can be polymerized to useful polymers. Simply by anhydrous acid catalyzed condensation or by metathesis.



Scheme 4

Obviously, one can use N-substituted maleimides or N-substituted 2H-pyrrol-5-ones as the dieneophiles. They would broaden the conceivable structures resulting in a variety of new dimer pyrrolidone analogs. Another approach to linear "pyrrolidone" polymers by metathesis might be as

follows:

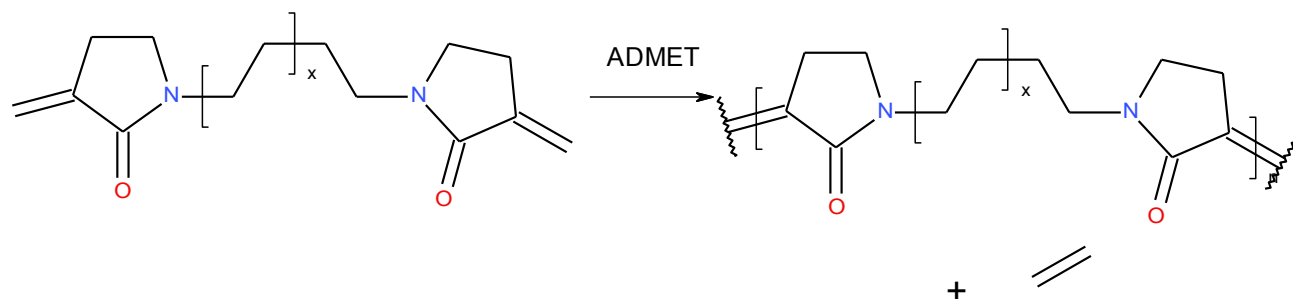


Scheme 5

I would think that 5-membered heterocyclics would be favored over large macrocycles and that the Diels-Alder reaction is considered a click reaction reliably resulting in a polymer. Bis-maleimides can also be employed.

Note that other isomers with the pyrrolidone carbonyls pointing in the other position after the Diels-Alder reaction can occur in all the above examples.

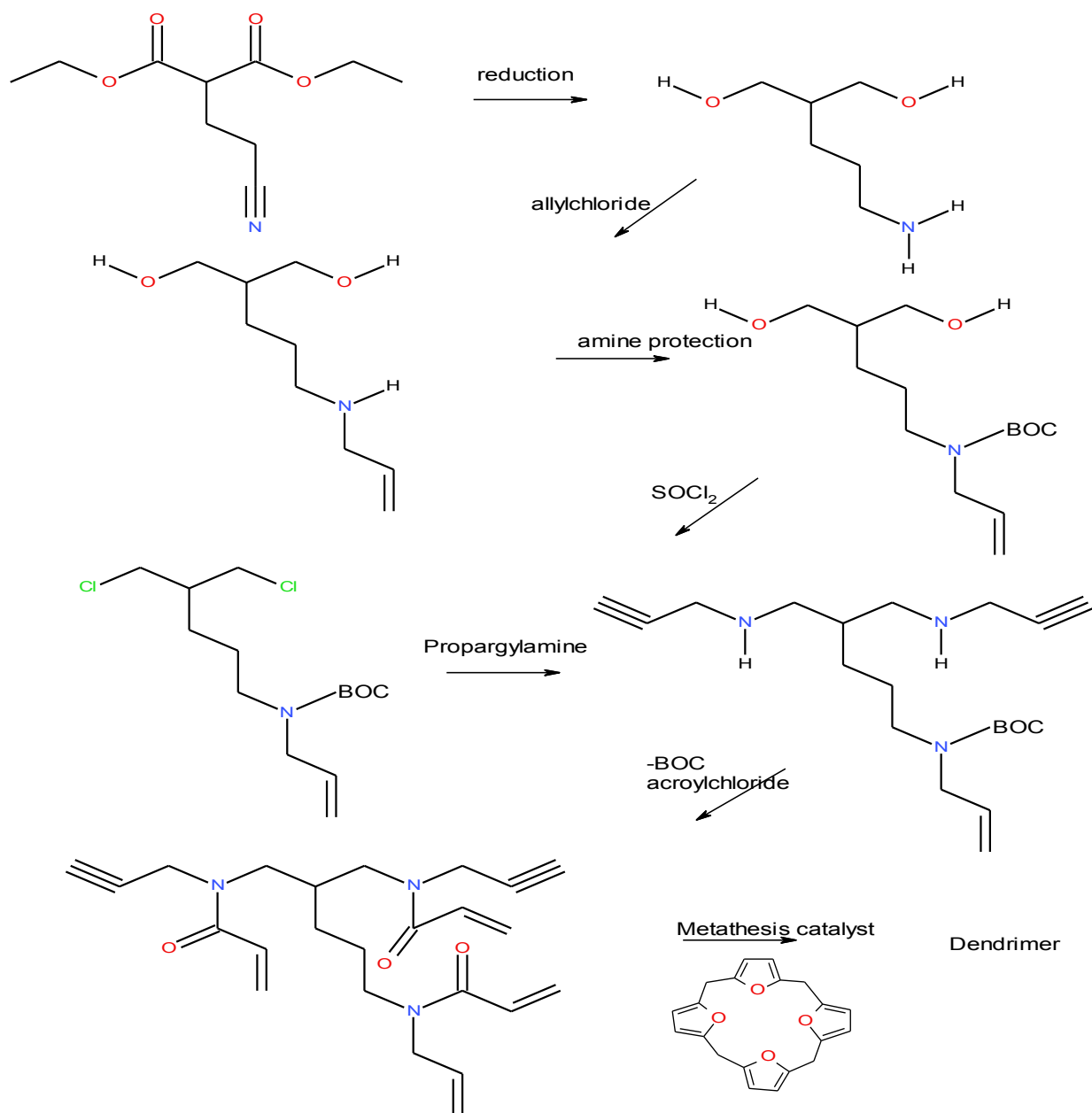
In addition, the 3-methylene pyrrolidone can be polymerized as a diamine dimer;



"Pyrrolidone" Dendrimer-like compounds

If you are following my reports on my web page (rloginconsulting.com) then you realize that I have a strong belief in the value of the lactam as a functional group especially the pyrrolidone ring because in this lactam the orbitals allow the best overlap for charge separation. This is why PVP is water soluble and able to complex anions like the triiodide and phenolics. This is why on my blog I have tried to figure out how to use it in a wide variety of compounds where I believe it has never been used before. I do this because I'm interested in it and because it deserves to be pursued. I would hope that the ever growing list of VP manufacturers and those who polymerize it in its various forms and grades would see the value of doing more innovative research involving new uses. Obviously I would love to be involved as a consultant.

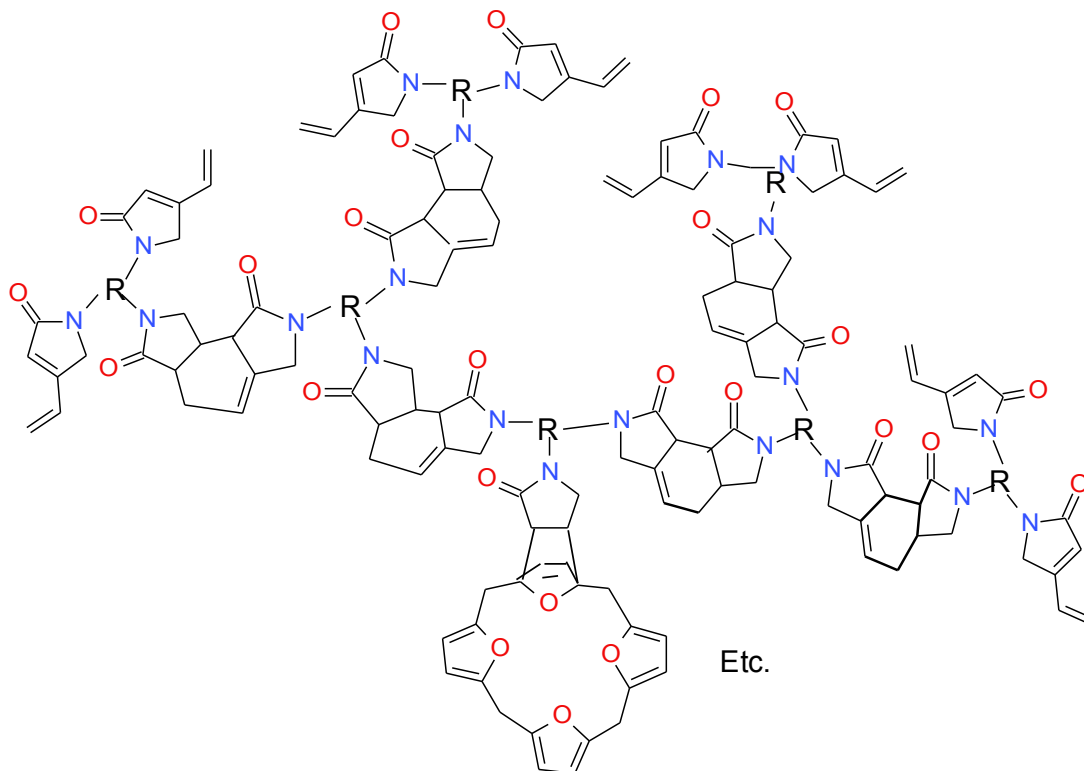
My first approach to a pyrrolidone "dendrimer" (actually hyperbranched polymers) is the following:



Scheme 1

Several problems can be visualized with scheme 1; the unsaturation could react by metathesis in unexpected ways to form large rings, the 3-pyrrolin-2-ones could isomerize to the 4-pyrrolin-2-one which might not enter the Diels-Alder reaction? Obviously other things can go wrong-but that is the nature of research. If the Diels-Alder reactions go as predicted then a partially growing

dendrimer would look like:

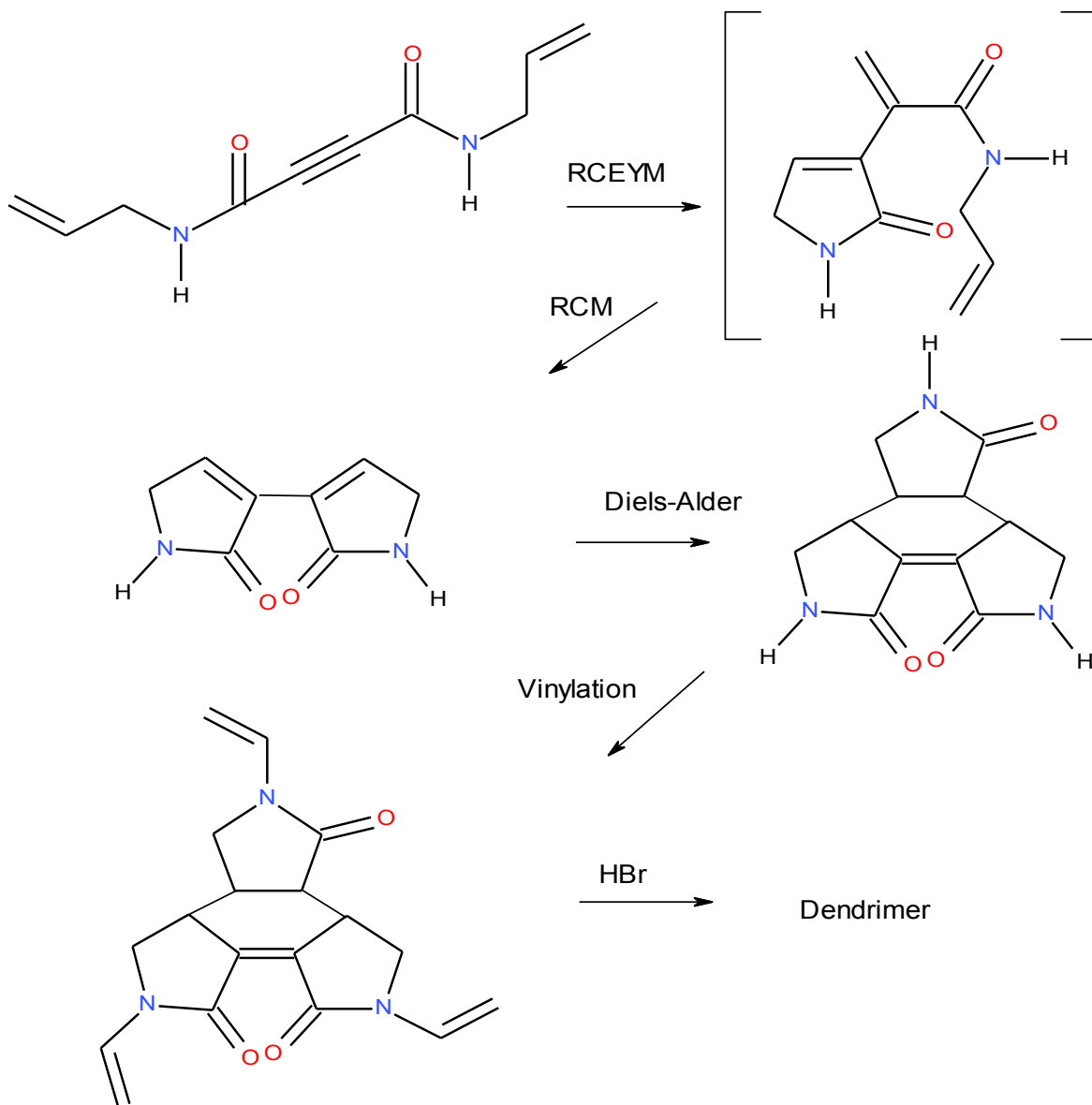


Scheme 2

Obviously, the build out is not so neat with chains growing at different rates resulting in chains of various lengths. They would not be as neat as some of the well known dendrimers, but dendrimer like. Actually the dendrimers are usually prepared stepwise by an iterative approach.

Another route to "pyrrolidone dendrimers" (actually hyperbranched polymers) is shown in scheme 3. In this case a double RCEYM takes place leading to a diene which is reacted with a preformed 2H-pyrrol-2-one. Obviously, these reactions are possible but they could take alternate routes. However a "pyrrolidone" dendrimer would be very interesting for a wide variety of uses, such as drug delivery, capture of and transport of DNA, scaffolds for enzymes, catalysis by carrying metal containing structures. I think the best approach to the utility of such dendrimers is to look at Prof. Tomalia et.al new book "Dendrimers, Dendrons, and Dendritic Polymers" Cambridge, 2012. He shows a wealth of Dendrimer uses some of which could be of

immense value.



Scheme 3

My concern is that the unsaturation from RCEYM might isomerize rather than produce a diene that would undergo the Diels-Alder reaction.

Remember, dendrimers and dendrons that are reviewed in Tomalia's book are prepared by complicated multistep procedures. The hyper branched polymers are simpler and can also have interesting properties. The point is to stimulate

thinking about new unique uses for the pyrrolidone functionality.

Conclusion:

Metathesis can lead to numerous compounds of value especially to those companies who are involved with PVP and all its variations. I would like to help any company that sees value in my ideas.

If there are mistakes in any proposed chemistry, I would appreciate your comments.

Thank you,

Dr. Robert B. Login

rloginconsulting.com