Pyrrolidone backbone polymers

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[0001] This application claims the benefit of United States Provisional Patent Application No. 61/744,343, filed 09/24/2012.

[0002] PVP (homo and co-polymers) are one of the most successful commercial specialty polymers. They are manufactured by only a few companies, chief amongst them are Ashland and BASF. Thousands of references and patents deal with all aspects of their chemistry; however, no other polymer type has successfully competed with them since they were introduced in the 1930's. But are they the best way to express pyrrolidone chemistry? An improvement would afford its creator a significant financial position with the ability to dominate the market.

[0003] The immediate goal of the following chemistry is to devise poly pyrrolidone's where the pyrrolidone is in the polymer backbone. Such polymers have not been investigated as plasma volume expanders in analogy with PVP. PVP, once thought to be the premier plasma expander, fell by the wayside because of toxicity problems resulting from the difficulty of it's elimination and hence retention in the body. Placing the pyrrolidone group in the polymer backbone presents the chance of developing a more easily eliminated polymer because their structure more closely resembles polypeptides. Kim et. al. USP 5,880,252 to BASF illustrates this very idea but apparently they have had limited if any success? I suggest that a competitive polymer should have about the same percentage pyrrolidone groups as PVP. The Kim patented polymers do not reach that level.

[0004] PVP has other important properties that would be mimicked by said poly pyrrolidones such as binding dyes, bilirubin, insulin, penicilliin and other drugs. “When infused intravenously, it increases the aggregation of erythrocytes and their

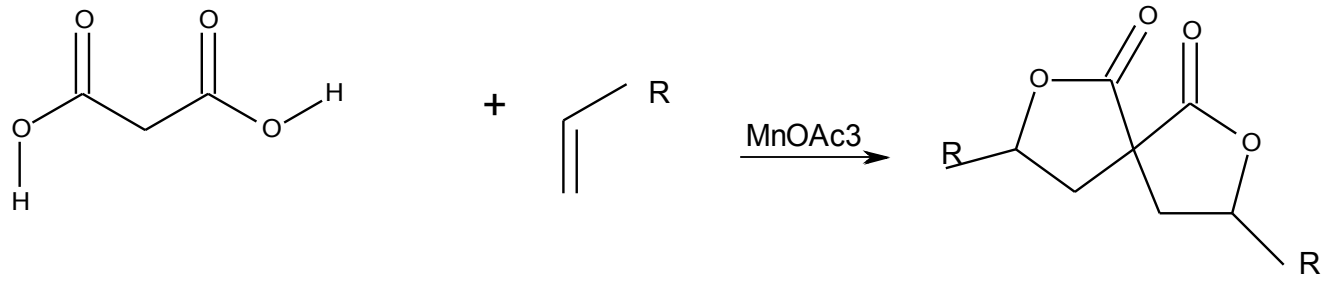
sedimentation rate but does not prolong the bleeding or clotting time. It decreases significantly platelet adhesiveness in human blood both in vivo and in vitro without altering the platelet count." etc (Sanbar and Smet, Circulation, Vol 38, Oct. 1968. p771). There are many other benefits of PVP and it's copolymers too numerous to mention. In fact PVP was once stockpiled in significant quantities during the Cold War to be used as a safe plasma expander. Currently a variety of plasma expanders are being tested, but they have one problem or another and that is why DOD is encouraging researchers by paying for the testing.

[0005] Pfirrmann, USP 6,080,397 clearly spells out the problems with PVP; namely, the inability of elimination. He shows how to limit high mw fractions in K-17 which he claims are the problem and that the low mw fraction is safe and easily excreted. I feel that PVP, even low mw polymers, have too much of a negative history to easily recover its position as a blood expander? That is why, a new approach employing pyrrolidone chemistry is required.

Approaches to poly pyrrolidones:

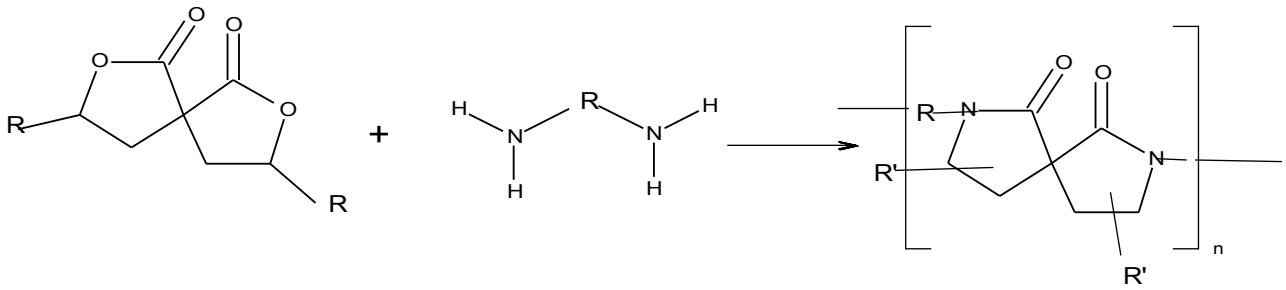
Bis-lactones and diamines;

[0006] 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.

[0007] Bis-lactones are availible and have been condensed with diamines but never to my knowledge promoted as plasma expanders? For example;



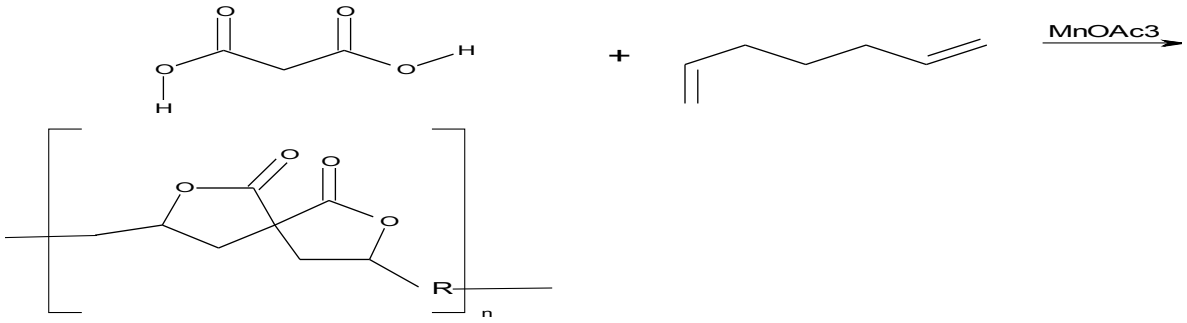
Cosar and Tanquary, USP 4,064,086 for similar compounds.
Jian-Qiang et. al. Chem J. of Chinese Universities, 2001, vol. 22, #5: 851-859.

When R=ethylene then this structure surpasses PVP in % of pyrrolidone and is the most direct approach to new plasma expanders.

[0008] A problem with this chemistry is to get the intermediate hydroxy-amide to close in high yield to the pyrrolidone. Conversion of this intermediate to a hydroxyl derivative with better leaving group characteristics accomplishes this cyclization. When heated to temperatures above 200C in a pressure reactor, this intermediate will eliminate water, producing a poly pyrrolidone backbone polymer. Conversion of the intermediate to an acetate ester with acetic anhydride allows the cyclization to occur under milder conditions. Other hydroxyl derivatives that are good leaving groups can also be considered.

Bis-Lactones:
[0009] Subsequent reaction of said spirodilactone with primary amines forms the spirodipyrrolidone derivatives. In the case of diamines, new poly pyrrolidones would result. Other types of bis-spirolactones have appeared in the patent literature and have been used to generate poly pyrrolidones but none have been claimed as key components of hair fixative formulations or as pharmaceutical excipients (tablet binders for example), and as components of synthetic blood substitutes.

Polymeric Bis-Lactones:
[0010] Also bis-alkenes with the unsaturated groups sufficiently separated by for example longer chain alkyl groups, or similar diacids, also form polylactones by this Mn(OAc)3 chemistry.

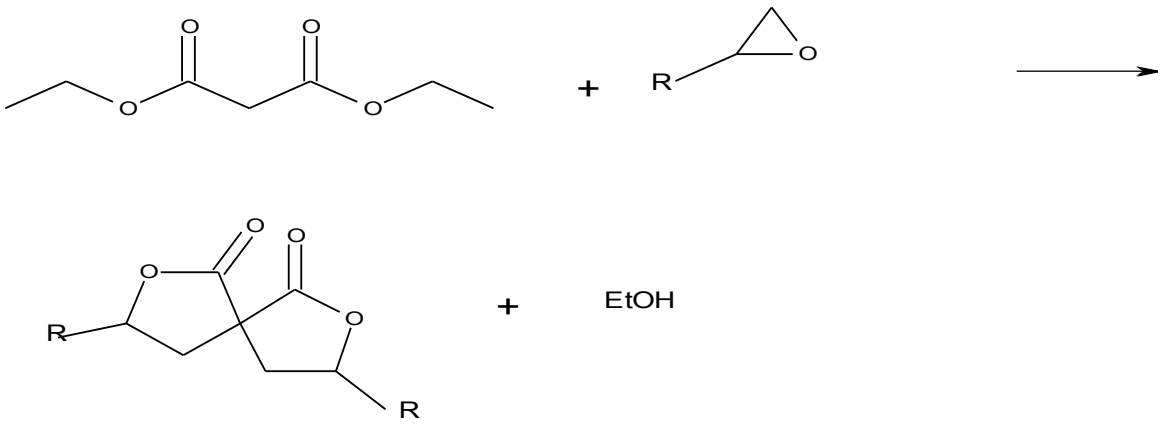


Subsequent conversion to the pyrrolidone increases the flexibility for designing said blood substitutes. Said polymers can also be employed in a variety of applications in competition with the PVP's.

[0011] Fluorined alkenes results in another valuable bis-lactone affording fluorine containing poly pyrrolidones. The amount of fluorine could be increased by employing flourine containing diamines. Such flexible chemistry connects the flourinated blood substitutes, known for their ability to carry oxygen and to remove CO2, with the plasma volume expander capability of these PVP analogs.

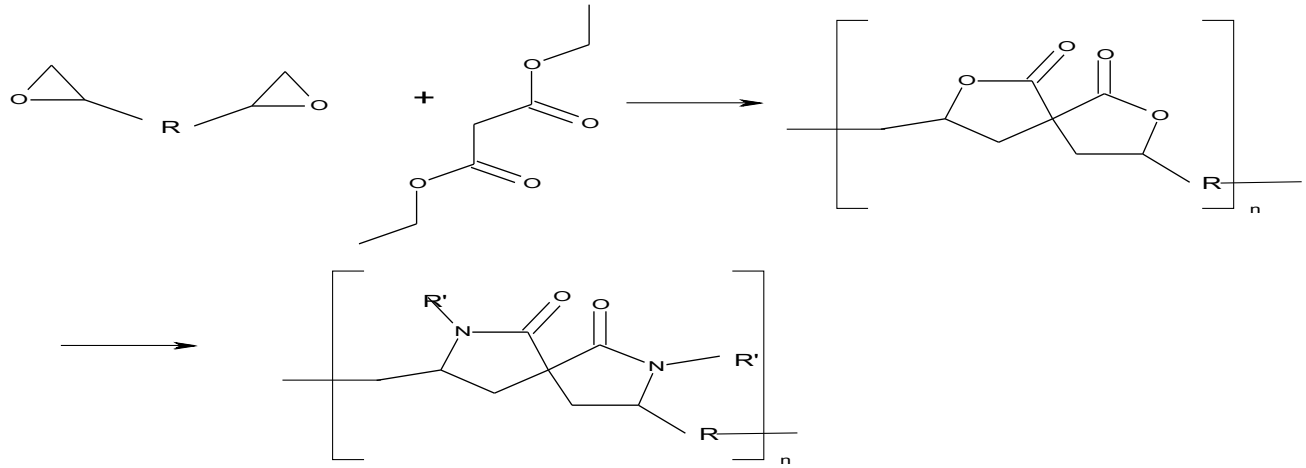
[0012] A problem with this spiro-lactone chemistry is the work-up. Presently, the initial reaction is run in acetic acid, the excess of which is washed out by separating the organic layer with water. A volatile solvent is used to facilitate the work-up. The specialty chemical industry would find this difficult; therefore, since quite a few of these spiro-dilactones are relatively high mp crystalline solids, they and said polymers will ppt out of the acetic acid. A second spiro-dilactone insoluble solvent can be added to the acetic acid to help the product to crystallize or in the case of polymers, ppt out. In this way a (automated) filter press easily recovers the product.

[0013] 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.

An additional advantage of this approach is that selected diepoxides will produce polymers.

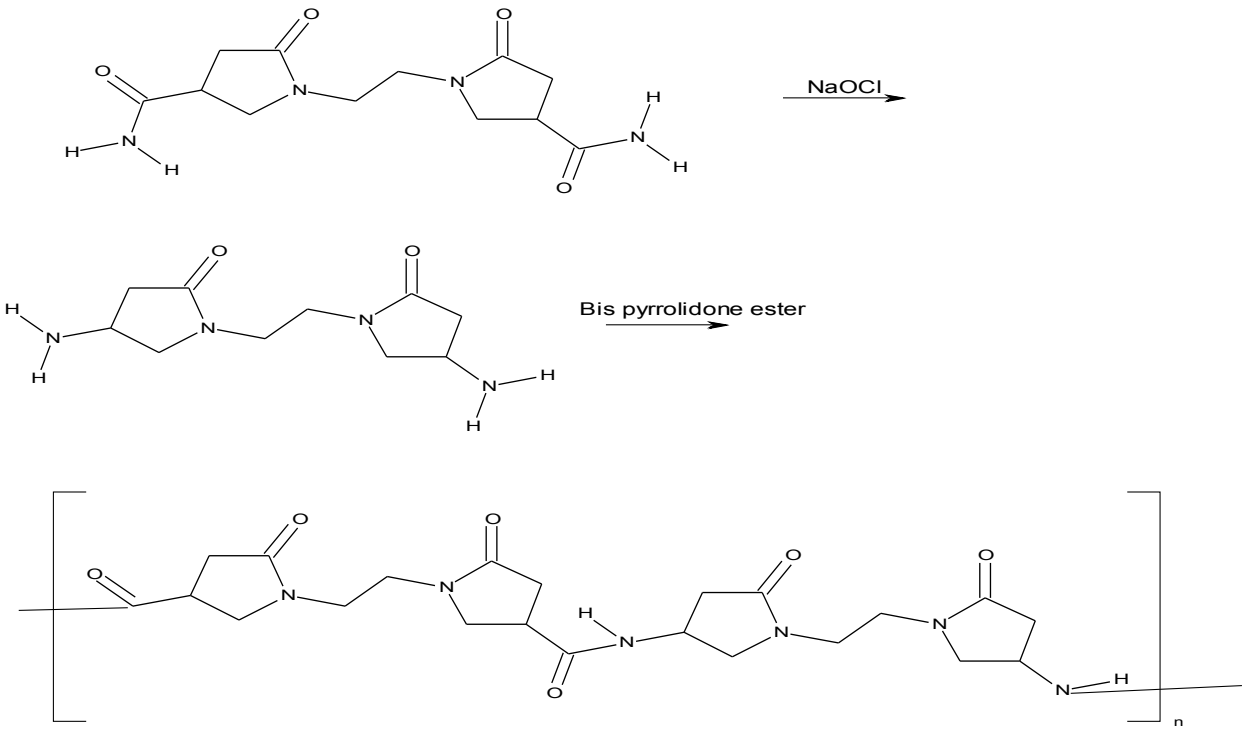


[0014] Such polymers can be esterified with ethanol for example resulting in polyhydroxy esters, that exhibit water solubility and the ability to cross link on dry down. This is in addition to said poly pyrrolidone based blood substitutes prepared by condensing said polylactone polymers with primary amines. The cyclization process is very similar to the same as the PVP types (N-octylpyrrolidone for example), high temperature cyclization in a pressure reactor. Temperatures of 175-250C are suitable.

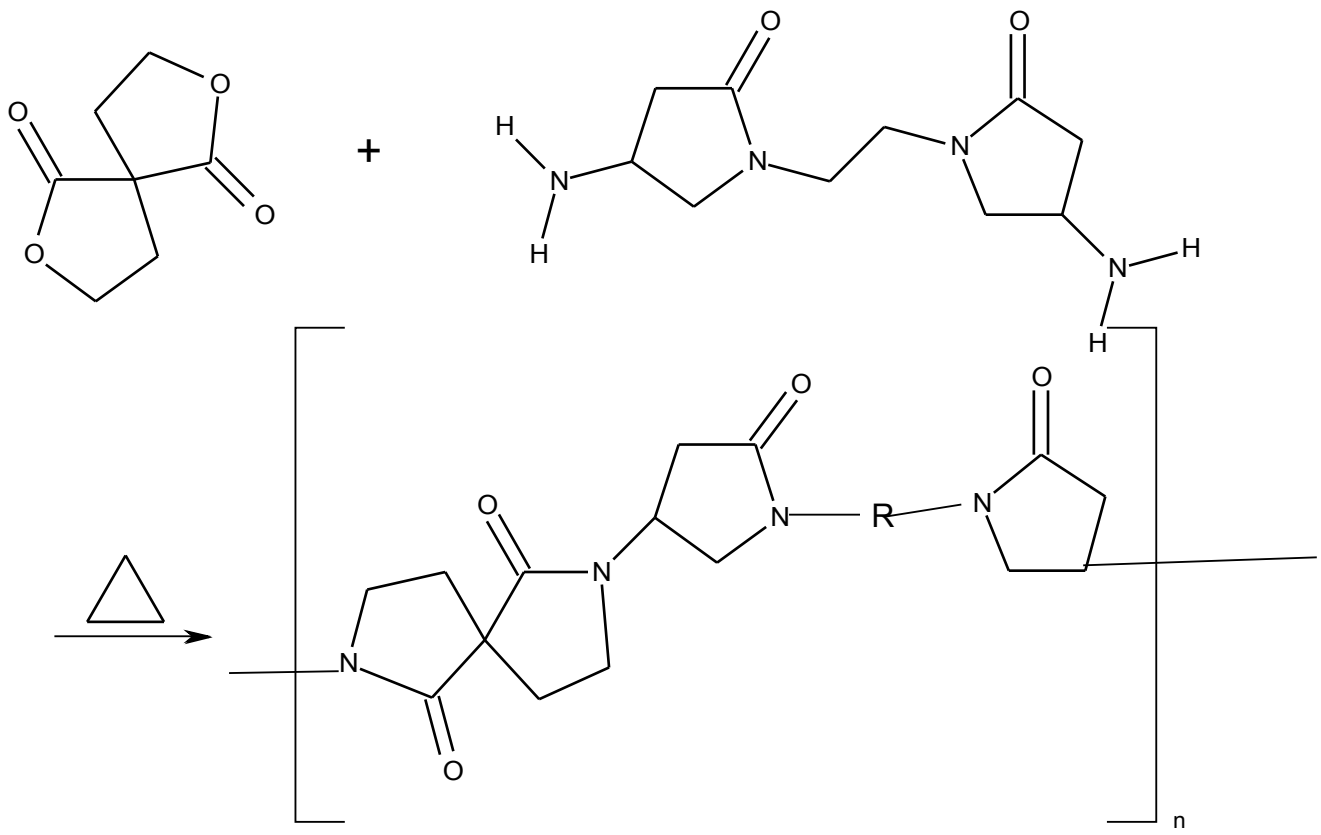
Itaconic acid derivatives:
[0015] There is a patent literature concerning the reaction of itaconic acid or its esters or

anhydride with diamines. Bavley et. al. USP 2,993,021 was the first to show that a mole of diamines such as ethylene diamine would react with methyl itaconate to form the bis-pyrrolidone, a crystalline compound, in high yield. The reaction is run neat and hence would be considered as a green reaction...no solvent and itaconic acid is made from renewable RM's. At least thirteen patents reference this patent including the previously mentioned USP 5,880,252 to BASF.

[0016] The bis-pyrrolidone ester when mixed with aqueous ammonia forms the diamide. Said diamide can be readily converted to a diamine derivative by the Hoffmann rearrangement. This diamine can be condensed with said dicarboxy bis-pyrrolidone to form a polyamide:

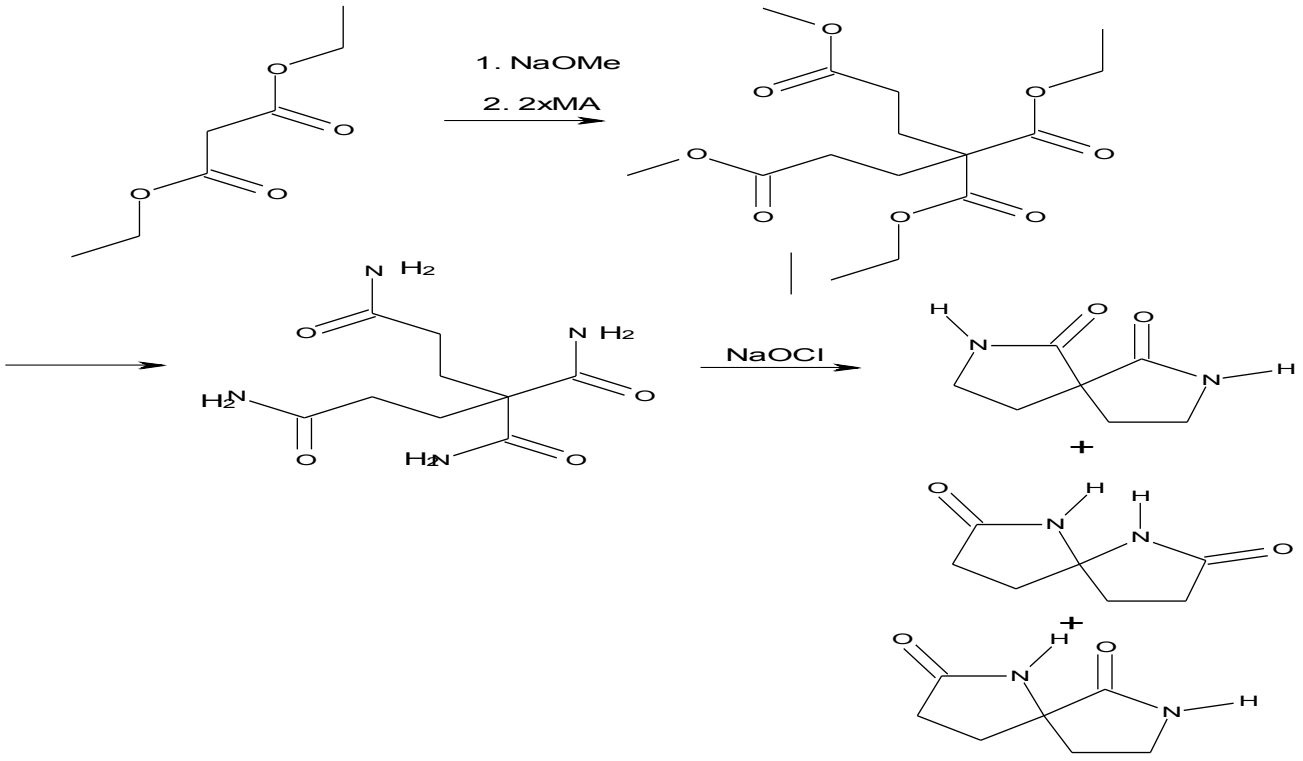


[0017] This polyamide-bis-pyrrolidone(PABP) has a % pyrrolidone back-bone structure similar to PVP. It is water soluble and mimics if not surpasses PVP in utility. Pyrrolidone is noted for it's complexing ability and PABP would complex CO2(carbonic acid) and possibly O2 to function as a complete blood substitute.

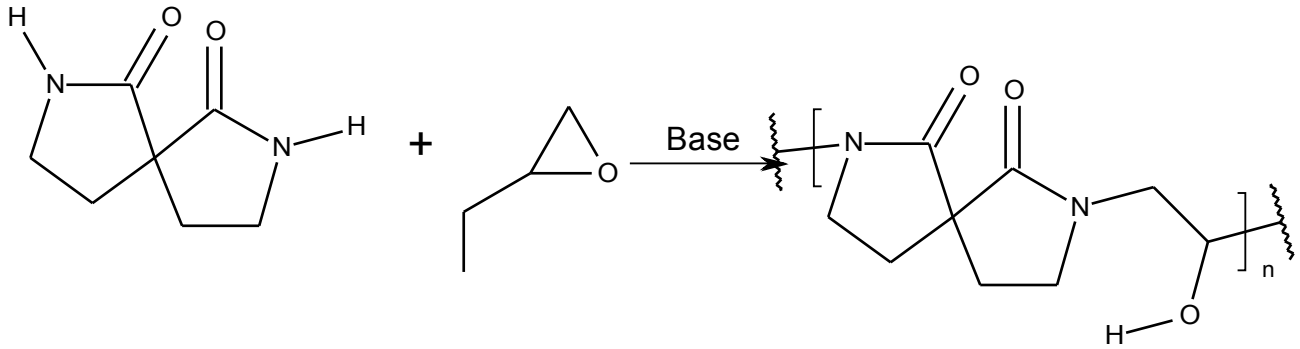


The bis-pyrrolidone approach (a version of PABP with a higher % pyrrolidone) can also be used with the di-lactones as illustrated above.

[0018] Another approach to spiro compounds also relies on the Hoffmann rearrangement. For example:



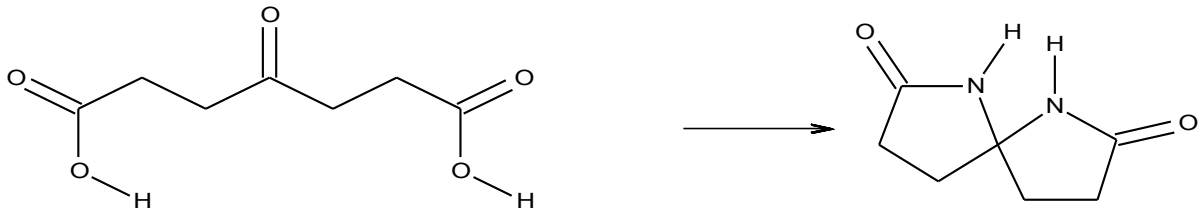
This requires that the tetraester ester groups will completely react with excess NH4OH aqueous solution. In one experiment it was found that the addition of ethanol resulted in a homogeneous solution that after standing formed a crystalline ppt. Reaction with hypochlorite results in the pyrrolidone derivatives and ammonia evolution. In the presence of base, such pyrrolidone dimers (which as has been shown previously can be prepared by several routes and however it is prepared it) will react with epichlorohydrin to form polymers:



Such spiro-polypyrrolidones (prepared from spiro-lactones or as above) have interesting properties such as water solubility, ability to complex a variety of compounds in a similar fashion as the PVP polymers, film formers, hair fixatives, excipients such as

tablet binders or disintegrates. Said polymers or similar polymers (employing terminal alkyl dihalides instead of ECH) with chemistry similar to that illustrated above, can be degradable and excretable overcoming the deficiencies of PVP.

[0019] There is prior art concerning related spiro-polylactam monomers and polymers. Notable is a series of patents of P.C. Wang for example USP 5028688 where the chemistry of the amides of 4-oxoheptanedioic acid forming [4.4]spirodilactam's are revealed:



The fact that two amide nitrogens are on one carbon is similar to ketals and exhibit similar chemistry such as ready hydrolysis in water to the corresponding ketone diamide. Suggesting that such polymers would not be suitable as PVP competitors.

[0020] The six menbered spiro-imides are known compounds prepared by cyanoethylation of several types of malonic acid derivatives. Conversion of these amides to the spiro-lactam was performed using diethyl bis (2-cyanoethyl) malonate by catalytic hydrogenation (Bell et. al. Tetrahedron Lett. 1993,34, 971; and Choi et. al., Bull Korean Chem. Soc. 1996, V17, No. 4, 395). On my web site, rloginconsulting.com, I present another way of preparing related spiro-imides.

[0021] Rather than repeating the above embodiments, I want to state that the component reactants of the chemistry illustrated above can contain other functionalities such as fluorine, other halogens, sulfur, silicone, aromatics, heterocyclics etc., as long as such ancillary moieties do not interfere with the basic chemistry so illustrated.

[0022] Example 1 Bis-Spirolactones general procedure:
To a stirred pressure reactor (autoclave), is added 2.7g of Mn(lll)acetate followed by 25ml glacial acetic acid. The mixture is heated to 70C and 0.26g of malonic is added. The reactor is sealed and a volatile olefin (in this case, 5mmoles) such as ethylene is added under pressure. The mixture is stirred for two hours at 70C, cooled and discharged and filtered free of Mn(OAc)2 and distilled under reduced pressure to afford a high yield of bis-spirolactone.

[0023] Example 2 Polyamide general procedure:

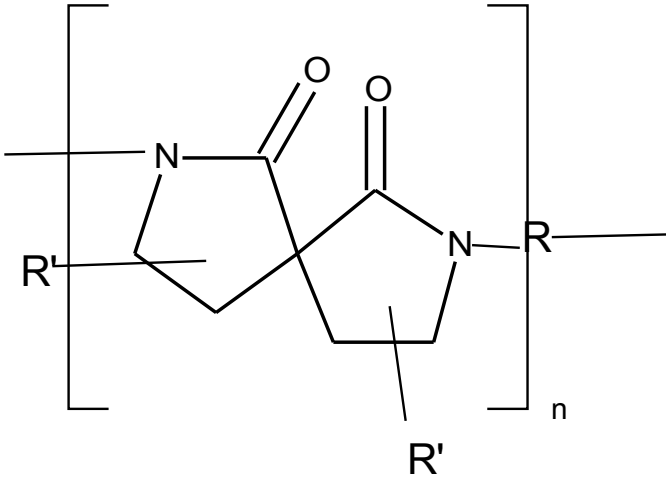
To the bis-lactone as prepared above in a stirred pressure reactor under a N2 blanket, is added an equivalent of freshly distilled diamine. The mixture is slowly heated so as to liquify the mixture if required. After 2hrs of stiring at the lowest temperture commenserate with homogenerity , the reactor is sealed and slowly heated to 250C where it is stirred and maintained at 250-275C for 4hrs. The mixture is cooled to 200C and carefully vented to remove water of condensation. If liquid, it can be poured out into a suitable container.

[0024] Example 3 Reaction of 2,7-dioxaspiro[4.4]nonane-1,6-dione (mp 108-109C) with amines:
Following general example 2, using said bis-spirolactone and ethylene diamine, a polymeric resin of light yellow color was obtained. Said polymer was soluble in water and could be dried down to film.

[0025] Example 4 reaction of 2,7-dioxaspiro[4.4]-1,6-dione with ammonia:
A 4 fold excess of NH4OH is mixed with a methanolic solution of the bis-spirolactone in a mag stirred sealed flask at room temperature. After two days, a crystalline solid appeared. It was filtered off and added to a pressure reactor and under N2. T
The reactor was sealed and slowly heated to 200-250C. After stirring for 4-6hrs, the mixture was cooled and discharged.

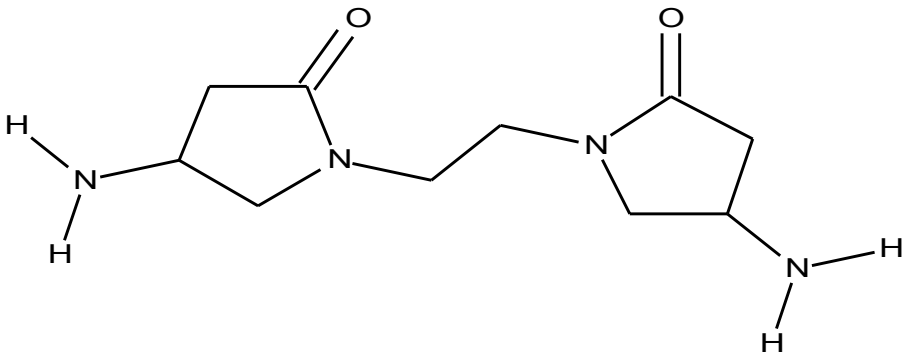
Claims:

1. A plasma expander polymer or synthetic blood component prepared from diamines and bis-spiro-lactones comprising the following repeat unit structure;

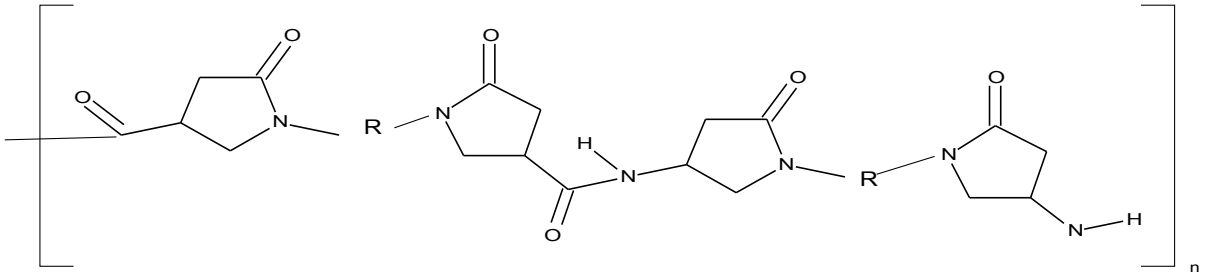


Wherein R=C1to C20 alkyl group and R'= H, or C1-C20 where both R and R' can be optionally substituted with other moities.
A diamine of the following formula;

2.A diamine of the formula;



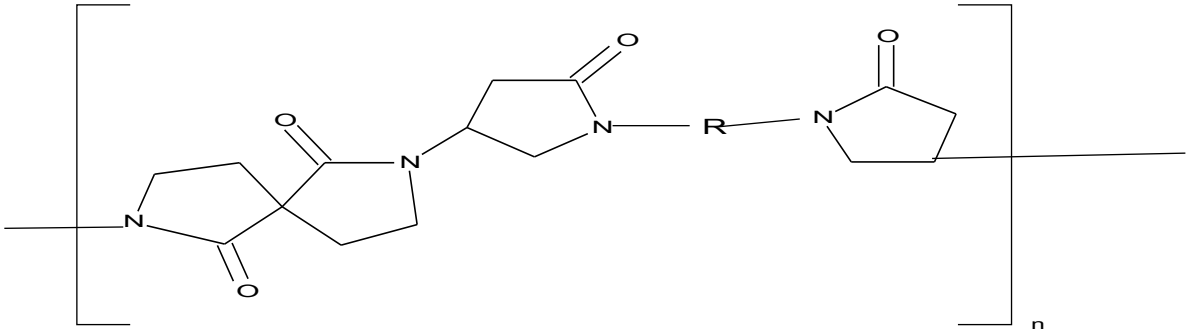
3. A polymer with pyrrolidone backbone groups comprising the repeat monomer residues with the following structure;



Where n=2-100 repeat units and R is a residue of a difunctional primary amine

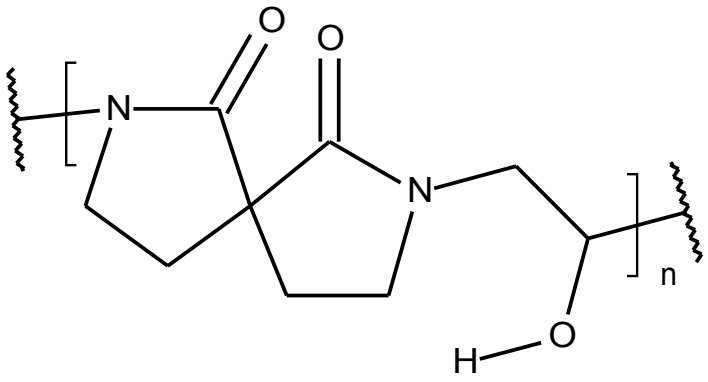
4'

A polymer with backbone pyrrolidone groups comprising the repeat monomer residues of the following structure;

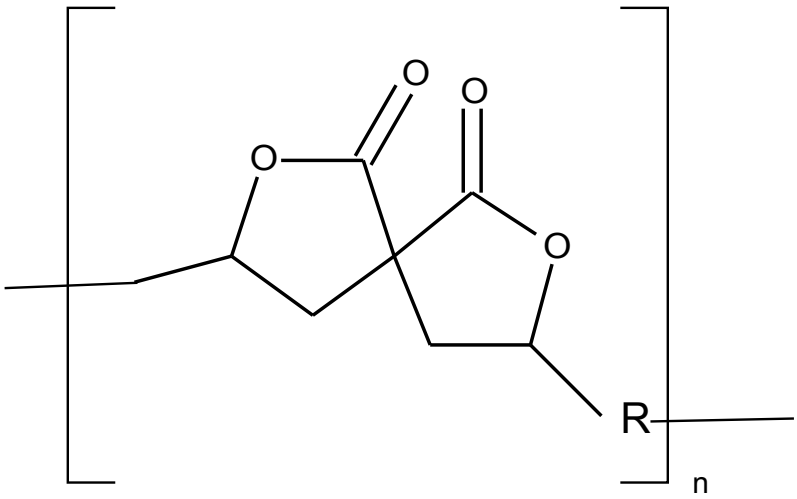


Where n=2-100 repeat units and R is an alkyl group of a difunctional primary amine.

5. A polymer containing backbone pyrrolidone groups comprising the repeat monomer residues of the following structure;



6. A polymer prepared from diepoxides and lower alkyl esters of malonic acid or alkyl dienes and malonic acid comprising the following structure;



In conclusion, the above examples may lead to a new beginning for pyrrolidone backbone chemistry.