Patent Application of Robert B. Login for Degradable Poly(acetal-lactone-ester) Polymers

This application claims the benefit of United States Provisional Patent Application Serial No. 61/630,604, filed December 15, 2011.

TECHNICAL FIELD AND BACKGROUND

[0001] This invention is in the field of degradable polymers, and relates generally to novel polymers and copolymers containing acetal, lactone, and ester linkages. The invention also describes bioerodible or biodegradable medical devices for delivering and internally dispensing beneficial agents to animals and humans in a safe and effective manner.

[0002] Degradable polymers that deliver pharmaceutical actives to target organs in a safe manner are reviewed in Polymeric Drug Delivery ll S. Svenson ed; ACS Symposium Series 924. A poorly soluble drug can be

carried by a polymer as a matrix of amorphous or micro crystalline or attached(pro-drug) formulations to a target organ overcoming solubility problems. In addition, said polymers can also afford protection and controlled release of the drug, preventing it from premature deactivation before reaching its target. Such polymers can contain hydrolyzable ester groups such as poly(D,L-lactide), Poly(D,L- lactide-co-glycolide), poly(e-caprolactone), and related polymers. Their disadvantage is that they are very expensive and being hydrophobic, slow to hydrolyze. Thus taking too long to be eliminated from the body after delivering the drug resulting in toxicity problems. This problem has been addressed by adding polyethylene oxide chains to said polymers to make them more hydrophilic. The poly(ortho esters) and anhydrides were also developed to solve this problem because they are readily hydrolyzed to small excretable molecules. However, they are difficult to prepare and they are very moisture sensitive and can prematurely hydrolyze before use. All of the presently available polymeric drug delivery methods have deficiencies chief amongst them is high cost. This technology needs an inexpensive readily and controllably hydrolyzable polymer that affords non-toxic byproducts that are easily removed from the body by excretion.

Background Art

[0003] The reaction of aldehydes and ketones with glycerol is well known to result in five and six membered cyclic acetals in very high yields (US2,680,735; 3,225,014; 3,714,202; 4,076,727). US 4,156,093 illustrates the potential for an acetal linkage connecting two glycerols together. US 4,876,368 and 2010/0216926 show that glycerol forms both five and six

membered cyclic acetals with a residual hydroxyl group that can enter into base catalyzed esterification with suitable esters. S. Selifonov et. al. US 2010/0292491 demonstrate that ultra low levels of typical acid catalyst is beneficial to the yield of ketals. US 2010/0222603 illustrates the well known fact that epoxides can react with selected carbonyl containing compounds to form acetals and ketals. Arnold (US 6,177,576) demonstrates the facile acid catalyzed formation of pyruvate glycerol ketals.

[0004] Pryde et. al. (US 3,183,215; 3,223,683, and 3,287,326) show that the monoester of glycerol prepared from unsaturated fatty acids can be ozonized to the monoglycerol fatty ester- aldehydes. This intermediate was reacted with methanol to produce the dimethyl acetal. Subsequent attempts to hydrolyze the ester under acidic conditions resulted in a low molecular weight poly(acetal-ester) polymers. Lenz (Macromolecules, V2, No 2, pp129-136, 1969) reviews the extensive work characterizing the preparation and cross-linking of poly(ester-acetals) of methyl azelaaldehydate dimethyl acetal with polyols such as glycerol. This study shows that it is obvious that this and similar carbonyl-carboxylic acids or esters will form acetals with glycerol and subsequently polymerize to poly(ester-acetals) as either homo- or copolymers. However, the ability of glyoxylic acid and glycerol to form poly(acetal-lactone-ester) polymers is unknown and unexpected.

[0005] However, in a series of US patent applications, S. Selifonov et. al. (US 2008/0242721; 2011/0021658; and 2011/0082264) actually use Pryde's said discovery to prepare a variety of poly(ketal-esters) from levulinic acid, a keto-carboxylic acid, versus the above said aldehyde-carboxylic acid; the

inherent chemistry being identical. WO 2009/032905 also claim the reaction of glyoxylate esters with glycerol as one of many possible reagents that can be used to react to form acetals and ketals. In this and other patent applications assigned to Segetis, Inc., no example of glyoxylic or pyruvic acid themselves are demonstrated. They assume that alpha-keto acids react the same as for example levulinic acid which as I have found is not the case! They do show the reaction of the methyl ester of pyruvic acid with glycerol but not pyruvic acid itself. The acid of alpha-oxoacid (glyoxylic acid is the only one) and alpha-keto acids do not react the same as other semialdehyde-acids or keto-acids and their esters.

[0006] US2,945,008; 3,092,597;3,424,726;3,714,291; 4,004,878; 6,740,376; and 7,064,169 illustrate that incorporation of an acetal or ketal linkage within a polyester backbone is known; however, the goals of this prior art was not to prepare polymers suitable as degradable drug delivery platforms. Most of these polymers are insoluble in water, very high in molecular weight, degrade to toxic byproducts and were not in anyway designed for said drug delivery application. Glycerol is reacted with levulinic acid or ester, in the Selifonov et. al. patents, to afford polyesters. They indicate that such polyesters are low molecular weight. They illustrate how to use this chemistry to prepare low molecular weight difunctional oligomers that can copolymerize with known polyester monomers. Said patent applications do not reveal my embodiments nor do they claim degradable medical polymer applications.

[0007] US 3,092, 597 claims that poly(acetal or ketal-esters) of , for example, spirobi(meta-dioxane) dicarboxylates can be subsequently

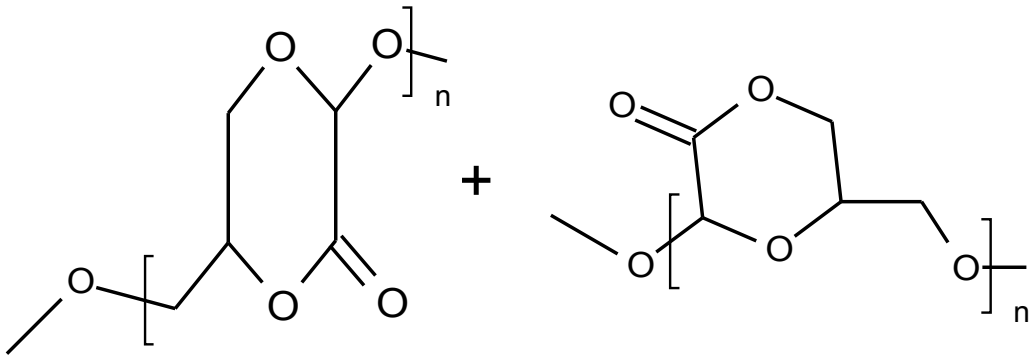
hydrolyzed to a water soluble mixture that can be cured with a acidic catalyst when dehydrated and heated to 150C.

[0008] US 2001/0021751 shows how glyoxylic acid can be used to crosslink hydroxyl containing polymers. The advantage is that glyoxylic acid is non-toxic and effective at relatively low levels vs the total hydroxyl content of the polymer. An explanation of this chemistry is not mentioned.

[0009] US 4144226 shows how alkyl gloxylates can be homo polymerized to polyacetals with pendant carboxylate esters without the involvement of the carboxylate moiety. Such polymers are used in the neutralized carboxylate form as detergent builders to replace phosphates. JP 10147640 shows how glyoxylate esters can react with ethylene glycol or epoxides to form polymers with pendant carboxylates also employing the well known ability of acetals to polymerize. These two patents highlight the requirement that a glyoxylate ester be employed. My discovery is for the use and utility of the free carboxylic acids of alpha-oxo or keto acids.

SUMMARY

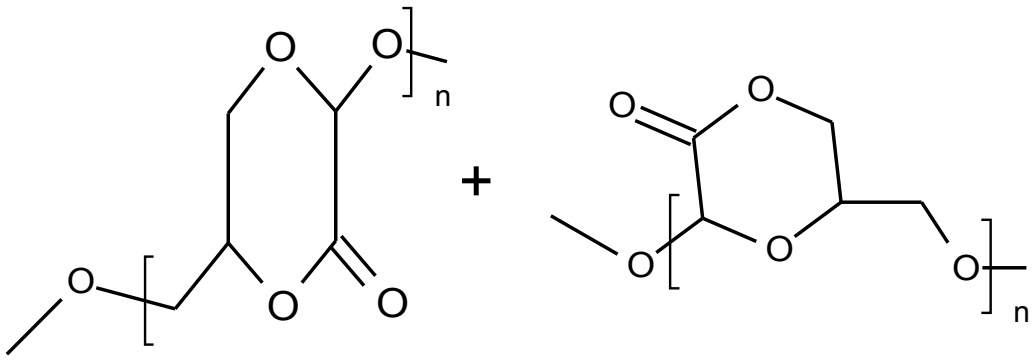
A random terpolymer poly(acetal-lactone-ester) comprising the formulas:



where N >1 and the said repeating units are randomly distributed in the polymer chains.

The compound of above wherein N is an integer from 2 to 100.

A process for preparing terpolymers of the above:



wherein n is as previously described, by mixing glycerol with glyoxylic

acid, in essentially equal molar ratios, and under conditions of heat and vacuum sufficient for removal of water of condensation from the reaction mixture.

The process above, wherein an acid catalyst such as protonic mineral acids like sulfuric, hydrochloric, or p-toluenesulfonic acid, or methanesulfonic acid, and the like are employed at minimum levels of 0.01-1.0 % necessary to accelerate the reaction.

The process of above, wherein a thermoplastic polymer is obtained.

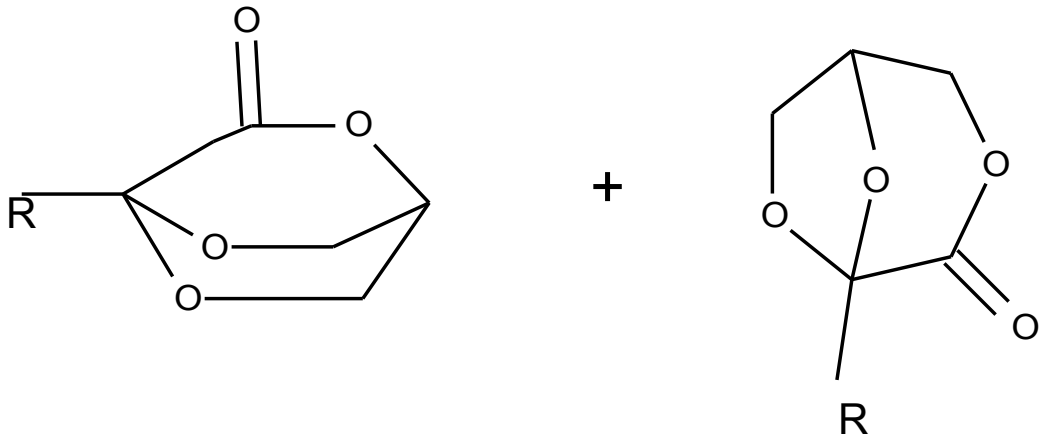
The process above, wherein the polymerization results in a thermoset polymer.

The process above, wherein at the thermoplastic liquid polymer stage, efficacious pharmaceutical drug ingredients and excipients are mixed into the polymer.

The process above, wherein said formulated thermoplastic terpolymer is further reacted to form a cross linked thermset polymer.

The said formulated terpolymer, either as a thermoplastic or thermoset, when added to aqueous body fluids, dissolves releasing said actives.

Compounds having the formulas:



wherein R is hydrogen or methyl.

The above compounds, wherein R is and alkyl group of 2-20 carbon atoms optionally substituted with aromatic, oxygen, sulfur, halogens, and silicone.
The above compounds, wherein R is an aromatic compound.
A process for synthesizing said bicyclic lactones comprising reacting said ingredients catalyzed by said acid catalysts at temperatures of up to 175C and vacuum such that two equivalents of water of condensation are removed and the said bicyclic derivatives are distilled under vacuum and collected.

The above process wherein the undistilled residue is hydrolyzed with water so as to reform the starting alpha keto-carboxylic acid and glycerol in order to reform the reaction products which can be again distilled under vacuum to generate a new batch of desired said bycyclic compounds.
The above process, wherein the said bicyclic ketal lactones are redistilled in order to obtain purer compounds.

The above process, wherein the said bicyclic ketal lactones are purified by recrystallization.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates bicyclic monomers formed in-situ from glyoxylic acid and glycerol.
Fig. 2 illustrates the synthesis of a typical poly(acetal-lactone-ester) terpolymer
Fig. 3 Is an infrared spectrum of a typical thermoplastic polymer of glyoxylic acid and glycerol (some overlap because spectrum is in two parts joined together).
Fig. 4 Is the H- NMR (d6DMSO) of the above polymer.
Fig 5A Is the H- NMR(CDCl3) of a bicyclic monomer of pyruvic acid and glycerol.
Fig. 5B Is the same above NMR expanded to show coupling details.
Fig. 6 Is the Infrared spectrum of the bicyclic monomer depicted in fig. 5.

Disclosure of the invention

[0010] The above references do not reveal the present embodiment. I have discovered that glycerol will react with glyoxylic acid (and not with alpha keto-acids) to form high yields of poly(acetal-lactone-esters) directly with and without acidic catalysis resulting in thermoplastic or thermoset polymers. Poly(acetal-lactone-esters) of glycerol and glyoxylic acid, hydrolyse in water to non-toxic byproducts at rates useful for the delivery of actives such as low solubility pharmaceuticals and or controlled release of said actives.

[0011] Said degradable polymers prepared from readily available inexpensive starting materials are superior to the currently used expensive polymers, containing ester or orthoester, or anhydride, or acetal linkages, that are currently of significant interest and highly valued for drug delivery. My poly(acetal-lactone-ester) polymers will do the same job at lower cost and their byproducts of hydrolytic degradation are known to be nontoxic, an extremely important advantage.

[0012] These and other advantages are achieved by poly(acetal-lactone-ester) polymers of glycerol and glyoxylic acid. The starting monomer structures initially generated are illustrated in figure 1. Not only can a homo-condensation polymer of said bicyclic acetal/lactone monomers be prepared, copolymers with other ROP (ring opening polymerization) monomers is also possible.

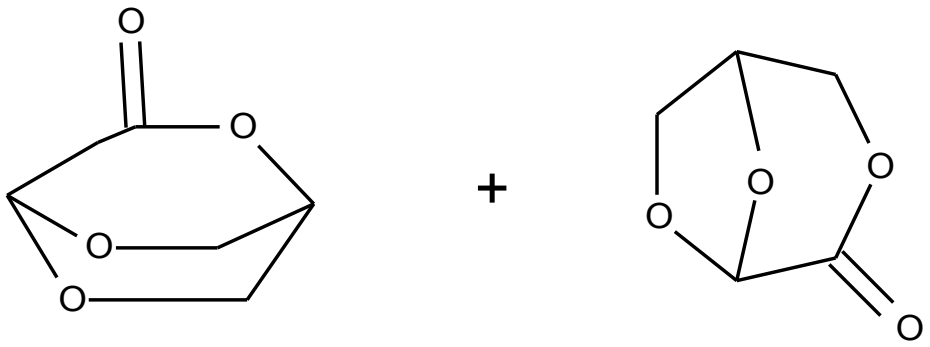


Fig. 1. Bicyclic intermediate monomers formed in-situ, readily polymerized under reaction conditions but not isolated.

[0013] Said polymerization reaction can be run neat without a solvent and employs one mole of glycerol for every mole of glyoxylic acid. Since the glyoxylic acid is trifuntional, as is glycerol, every functional group can theoretically react. The cyclic acetals as previously reported form in very high yields. These acetals should have one alcohol group and one carboxylic acid left over to react to form esters. If they were the only species present then gelation would not occur. This is not the case, when the polymerization is pushed to very high conversion and temperatures of 130-140+ C and high vacuum, gelation will occur. The polymerization is easily stopped before the gel point is reached. The resulting thermoplastic product is clear of low color, hard and non-blocking. At this stage, it can be formulated with pharmaceutical actives and necessary excipients resulting in unique degradable drug delivery formulations.

[0014] Attempts to analyze said polymers are difficult, as they are at 25C or RT, slowly(time for dissolution depends on MW and degree of cross-linking) soluble in water and alcohols, but dissolution results in degradation as residual carboxylic acid groups can cause hydrolysis. Sodium bicarbonate aqueous solution can be used as a mild neutralizer followed by rapid titration with 1N HCl which indicates 42% ester and 58% carboxylic acid groups. This is very much like the ortho-ester degradable polymers that must be kept away from moisture in order for them to be stable. They are stable solids when moisture free as are the polymers of this embodiment.

[0015] Continued exposure to sodium bicarbonate solution (known to not cause the hydrolysis of acetals, and to be a weak reagent for the hydrolysis of carboxylate esters) results in the titration of most of the theoretical

carboxylic acid originally in the dry polymer before its exposure to said aqueous solution.

[0016] Infrared analysis (fig. 3) of melted polymer films on salt discs show OH, ester at 1745-50cm-1, and typical acetal signals around 1200cm-1 and not much more. This indicates significantly more ester linkages than the initially titrated 42%. Suggesting that the OH absorptions are a combination of hydroxyl and carboxylic acid OH groups. NMR of a sample of said polymer taken in d6 DMSO reveals a complex set of absorptions in the expected regions of the spectra for lactone, ester and acetal (fig. 3). The NMR(fig.4) also shows very little COOH at 9.1ppm which I ascribe to acid's proton.

[0017] When this reaction is attempted with ethyl glyoxylate and glycerol, catalyzed with H2SO4, gellation occurs almost immediately at relatively low temperatures of 110-120C and 24"Hg vacuum. This is radically different than that experienced with glyoxylic acid and can be attributed to the greater availability of the ester to cross linking while the carboxylic acid more readily reacts to form a lactone as explained below.

[0018] Not to be limited by theories; however, my interpretation of the fate of the carboxylic acid groups is the formation of lactones with acetal linkages as illustrated in fig. 2 . This was not as expected from the five and six membered acetal acid starting monomers suggested from the Selifonov patent applications and the prior art. The acetal can readily polymerize with the lactone retarding polyester formation. Poly(acetals) with pendant six membered lactones can eventually polymerize through the lactone (Okada

et. al.; Macromolecules 1986,19,953-959). Said lactones can crosslink with either each other, and/or free hydroxyl groups, and can generate free acid on exposure to water even in the presence of bicarb basic aqueous solutions. These observations are commensurate with the apparent minimal amount of carboxylic acid by NMR and the symmetrical carbonyl absorption in the infrared at approximately 1750cm, being exactly where a six membered lactone band would absorb. My evidence also suggests a bicyclic intermediate. The lactone forms when the hydroxyl of the glycerol is in the correct stereo-position as any other position would be strained:

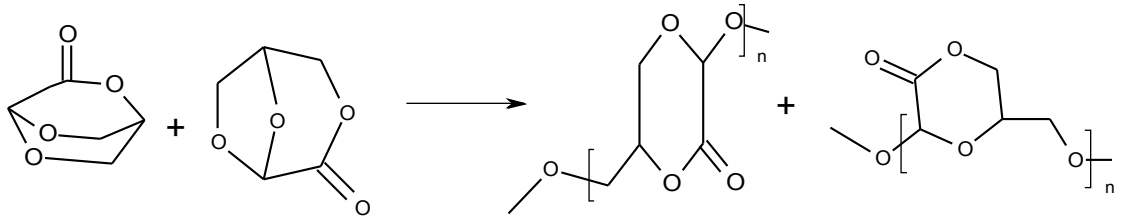


Fig. 2.- Bicyclic starting monomers and some repeat units of the thermoplastic polymer.

[0019] The bicyclic structures are intermediates, then they could be used in-situ and undergo copolymerization with for example typical ROP lactone monomers. The polymerization of said glyoxylic acid might, for example, be followed by gc and when the maximum generation of bicyclics was achieved, said ROP lactone monomers could be added along with a catalyst like stannous octoate. Residual acids groups would function as the site of initiation.

[0020] When the same reaction is attempted with pyruvic acid, little polymerization occurs. With H2SO4 catalysis, under the same conditions as employed with glyoxylic acid, there is no viscosity increase and when the reaction mixture is placed under 29+"HG vacuum, a crystalline product distills over at high reaction mixture temperatures (160-180C,pot temp.) followed by a higher bp compound(bp 90-120C and 120-140C for each, at 29+"Hg). When high vacuum is employed, about 50% of the initial charge will distill over as an approximately 60/40 wght % mixture of crystalline compounds. GC analysis shows both compounds elude close together, indicating that they are similar. The crystalline compounds were recrystallized from methylene chloride to afford transparent white plates with a mp of 60-65 C. H- NMR in CDCL3 reveals the spectrum in fig.5 A&B . These spectrums are exactly as expected for the indicated structures. Infrared is also as expected (fig.6). This result is radically different that those in the prior art especially those claimed in Selifonov's recent applications (previous cited). They also strongly support bicyclic intermediates as part of the polymerization mechanism for the said reaction of glyoxylic acid and glycerol.

[0021] The reason for the lower reactivity of pyruvic acid to the expected polymerization with glycerol is because the methyl group sterically interferes with this reaction. Glyoxylic acid has no steric hindrance and therefore, when a bicyclic intermediates forms, it quickly enters into the polymerization. Other non-alpha keto or oxo-acids(semialdehydes) would not work in this reaction to form lactone containing acetal-polyesters because the lactone structure would not be favored because of excessive ring strain. Selifonov's patent application does reveal a similar bicyclic ketal-

lactone of leuvinic acid and glycerol that they generate as a degradation product (at very high temperatures) from the corresponding polyester. Such bicyclic lactone ketals can be polymerized by ring opening polymerization (ROP) procedures. Said bicyclic lactone ketals generated from pyruvic acid and glycerol could also be homo and copolymerized with typical ROP monomers (see US 2009/0118459A1; J. Feien et. al., May 7,2009 for examples).

[0022] The polymerization of glyoxylic acid and glycerol is unique and unknown. It will form thermoplastic polymers of significant molecular weight, resulting in relatively hard thermoplastics. The polymerization can even be pushed to form thermoset resins. Gelation occurs at relatively high conversion where a few cross-links can be effective. If facile cross-linking were actually occurring, gelation would be accelerated during polymerization as the number of reactive polymer terminals increased and the gelation would be hard to control. This is not the case and shows that lactone moieties are stable and preferred to chain esters, even though some chain esters must also be part of the polymer's structure. H-NMR of this polymer is very complicated but does show the expected general locations of absorption bands (fig. 4).

[0023] The said polymers are soluble in water and alcohols and this is due to facile hydrolysis. However, at the earlier thermoplastic stage, they are soluble in dry DMF and NMP showing no sign of gel. When cross-linked, they form gels in such solvents. Said polymers melt to flow-able liquids when thermoplastic but turn brown from oxidation when converted to cross linked thermosets.

[0024] The thermoplastic stage polymerization can be performed in said anhydrous solvents, but running the polymerization neat works very well and avoids unnecessary work-up and cost of using solvents. Using commercially available 50% aqueous glyoxylic acid results in water being the only byproduct of any consequence. My process is an example of green chemistry as no dangerous byproducts are formed and the ingredients can be manufactured from renewable commodities.

[0025] As mentioned, the polymers of this invention can be mixed as solutions in solvents or as molten liquids with pharmaceutical actives and cooled to form microcrystalline or amorphous actives mixtures that will readily dissolve with time in various body fluids. They could also be implanted or injected into a target such as a cancerous tumor. A formulations containing said polymers could also include additional auxiliary excipients to enhance the formulations. Such auxiliaries can be pH regulators, binders, disintegrants etc. Said polymers are liquid at temperatures of approximately 80-130C so that formulating by adding to such liquids would not be a problem, as long as said pharmaceuticals and excipients are stable at such temperatures. As thermo-plastics, said polymers are soluble in selected solvents and can also be formulated with pharmaceuticals and excipients in solution.

[0026] HPLC analysis indicates that said polymers as thermosets will completely dissolve in a few hours in water and completely revert to starting glyoxylic acid hydrate and glycerol in 24 hours at RT. Similar dissolution profiles would be expected in body fluids. Glycerol and glyoxylic acid are

actually found in mammalian metabolism and are therefore non-toxic. It would however be a problem for those suffering from the rare hyperoxaluria where glyoxylic acid generates oxalic acid (for example see P.Baker et. al. AM. J. Physiol Cell Physol 287; C1359-C1365, 2004). Under normal metabolism, the body has no trouble with glyoxylic acid metabolism and it's conversion to excrete-able byproducts.

[0027] Many examples of alpha-keto mono and diacids exist other than pyruvic acid. For example phenylpyruvic acid, alpha-ketoglutaric acid, alpha-ketobutyric acid, phenylglyoxylic acid, alpha-ketoisocaproic acid, ketomalonic acid, alpha-ketoadipic acid to name a few. Such keto-acids will react with glycerol under said reaction conditions. Those based on monoacids would be expected to form bicyclic compounds; however those based on diacids afford highly cross linked polymers. For example, alpha-ketoglutaric acid and glycerol are known to form strong elastomers just by heating them together even without a catalyst (Barrett and Yousaf, Macromolecules 2008, 41, 6347-6352). I speculated that keto-diacids having reactive groups on either side of the cyclic ketal would not have the steric limitation of mono-ketoacids in which the acid must be on the same side of the cyclic ketal as the hydroxyl group for the bicyclic to form. Ketomalonic acid would have the same acid group on either side so it should react to form bicyclics in very high yields. Unfortunately, ketomalonic acid is very expensive and unlike glyoxylic or pyruvic acid, which are known to be nontoxic and part of metabolism, of unknown toxicity. Alpha-ketoglutaric acid is also part of metabolism and is non-toxic but as mentioned above, doesn't polymerize like glyoxylic acid. An attempt to use it in said reaction

identical to the procedure employed with glyoxylic acid, quickly resulted in a hard rubbery gel.

Example 1 Glyoxylic acid and Glycerol:

[0028] On a one to one molar basis, 50% aqueous glyoxylic acid and glycerol are mixed together to form a homogeneous solution. A strong acid catalyst such as sulfuric acid can be added at this point (relatively small amounts of sulfuric acid will accelerate the reaction and can reduce the color of the final product; on a 250gram scale, six drops of conc H2SO4 was sufficient) or the reaction can be conducted without a catalyst. The mixture is heated in a suitable multi-neck round bottom flask equipped with a heating mantle, a thermometer and a distillation take-off consisting of an overhead thermometer, condenser and receiver equipped with a vacuum take-off. In order to facilitate water removal, vacuum can be applied from the beginning of the application of heat. As water is removed, the temperature of the reaction mass increases such that a final temperature of 130-140 C is maintained under vacuum. When this temperature is reached at say 25" Hg vacuum, the mixture will thicken. When the mixture becomes difficult to mix because of frothing caused by the difficulty of bubbles of gaseous water to escape, the mixture is dropped out into a suitable container. This first stage can take from 1-4 hours or so and if a thermoplastic polymer is desired, then this is that product.

[0029] If a thermoset polymer is desired then the hot liquid reaction mixture is placed in a vacuum oven or desiccator at 110-140 C and 29+ "Hg vacuum to finish reacting. This takes 1-3 hrs. The final product is a hard plastic that is slightly to non- tacky and if exposed to moisture becomes very

tacky or liquid over several hours. When added to water, it will slowly dissolve. When added to sodium bicarbonate solution bubbling at the plastics surface is evident if the molecular weight is low; however, as the reaction goes to completion, solubility in water or dilute sodium bicarbonate solution slows considerably. Even in dilute hydrochloric acid, dissolution can take up to an hour.

[0030] As the condensation polymerization proceeds, the polymer is readily flow- able and liquid at the reaction temperature. Upon cooling it turns into a hard slightly tacky plastic but if pushed to completion by high vacuum (29+ " Hg) and 140 C, it can not be melted and therefore is cross-linked into a thermoset polymer. Said polymerization when catalyzed by a small amount of concentrated sulfuric acid forms a cross-linked thermoset polymer more readily than when the catalyst is not employed.

[0031] In this embodiment as a drug delivery polymer, actives can be added at any time before the final stage before the polymer becomes a thermoset. Other excipients can also be added at this stage, for example to neutralize the acid catalyst. The temperature of the polymerization can be adjusted to the stability of the drug active. And if lowered, the polymerization reaction can take much longer. At the completion of the polymerization, if the polymerization is stopped at the flow-able thermoplastic stage, the molten mass can be shaped into any desirable form. If pushed to a thermo-set, the polymer can be cooled and crushed to a powder. Said powder can be pressed with excipients and actives into, for example, pill form.

Example 2: Reaction of Ethyl Glyoxylate with Glycerol

[0032] In the same equipment described in example 1, A 50% solution of ethyl glyoxylate in toluene obtained from Alpha Aesar and used as received, was mixed with glycerol on a one to one mole basis.

A small amount of conc. H2SO4 is added and the toluene is removed at low temperature under vacuum (70C pot/ 50C overhead). When the temperature starts to increase to 80-90C, the mixture clears and starts to thicken. At 100-110C and 24"HG it is very thick and then suddenly gels and becomes an unstirrable mass. This is very different the glyoxylic acid under the same conditions as detailed in example one.

Second Embodiment: Formation and Utility of bicyclic ketal lactones.

Example 3: Reaction of Pyruvic acid with Glycerol.

[0033] In the same equipment as described in example 1, one mole of pyruvic acid and one mole of glycerol are condensed with the aid of a acid catalyst such as sulfuric acid to form a mixture of products resulting from the removal of two moles of water. The mixture is heated and placed under vacuum to remove the water of condensation. Usually this stage would be completed after an hour or two at 100-130C and 25"Hg vacuum. At this point, the temperature and vacuum can be increased to 130-160C and 29+"Hg. As the temperature increases from 130C, a distillate will come over into a suitable receptacle. The overhead temperature of the crystalline distillate was 90-120C, a second compound distills at 120-140 at best vacuum. When the overhead distillation temperature noticeably rises above 120C, the mixture is cooled and brought to atmospheric pressure. Two moles of water are added based on the pot residual mass. The idea is to regenerate the starting pyruvic acid and glycerol. After this occurs as determined by gc

or hplc, the vacuum is reapplied and the above process is repeated. This results in another crop of bicyclic crystalline ketal-lactone containing distillate. This process can be repeated over an over but at some point fresh RM's will be needed because of the greater efficiency of a larger pot charge. However, if the pot residue is allowed to go above 165C then a rapid gelation can occur, the nature of which is unknown but because phenothiazine inhibits this gelation, I speculate that pyruvic acid can react with itself to form an alpha hydroxyacrylic ester that can polymerize by a free radical mechanism.

[0034] By this method, yields of up to 60% of a mixture of crystalline isomers has been obtained. Analysis of the higher bp compound shows hydroxyl and carbonyl groups in the infrared suggesting it is the ketal-carboxylic acid adduct that resists polymerization under the same conditions as employed in the case of glyoxylic acid.

[0035] Molecular models clearly show that the carboxylic acid and alcohol groups must be on the same side of the ketal ring structure in order to be in a position to form the desired bicyclic monomers. This is the case with the pyruvic acid/ glycerol reaction unlike the glyoxylic acid/glycerol reaction which is much more reactive. Adding back water to regenerate the starting pyruvic acid and glycerol and then reforming the ketal-lactone mixture creates another batch of bicyclic monomer that can be recovered by vacuum distillation. Selifonov (US 2008/0242721) shows how to prepare a similar bicyclic monomer from levulinic acid or esters and glycerol. Since these bicyclics are large presumably strained ring structures, hash conditions of 280-300C at very good vacuum (0.08mm) were required. A further

disadvantage is that there is no mention of a method to increase the yield of a desired bicyclic. In addition their bicyclics are low melting waxes that must be purified by distillation under conditions not favorable to large scale production.

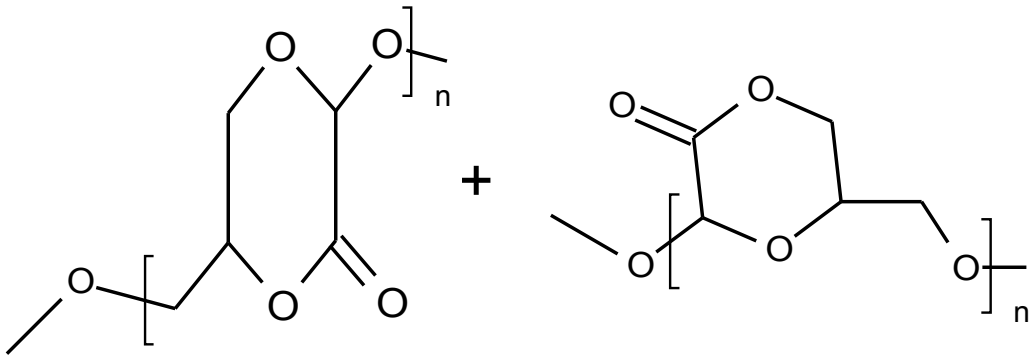
[0036] The said bicyclic ketal-lactone can be recrystallized from methylene choride as previously mentioned. It has a pleasant odor and is soluble in a variety of solvents this suggests their utility as perfume ingredients. It has a structure believed to be suitable for ROP (ring opening polymerization) and should undergo such ROP with basic catalysts such as stannous octoate plus initiator. But of greater importance, said bicyclic ketal-lactone could be copolymerized with other monomers that are employed in ROP polymerizations to afford ketal linkages that can be readily hydrolyzed when used for drug delivery. With sufficient incorporation of said bicyclic monomer in copolymers, results in polymers that can more readily degrade in the body, producing smaller fragments easily excreted in the urine. This would be of significant value and utility!

[0037] The above examples are not meant to be limiting as someone skilled in the art would see other obvious possibilities inherent in this disclosure.

CLAIMS

I claim:

1. A hydrolytically degradable, random terpolymer poly(acetal-lactone-ester) comprising a mixture of repeating unit formulas I and II:

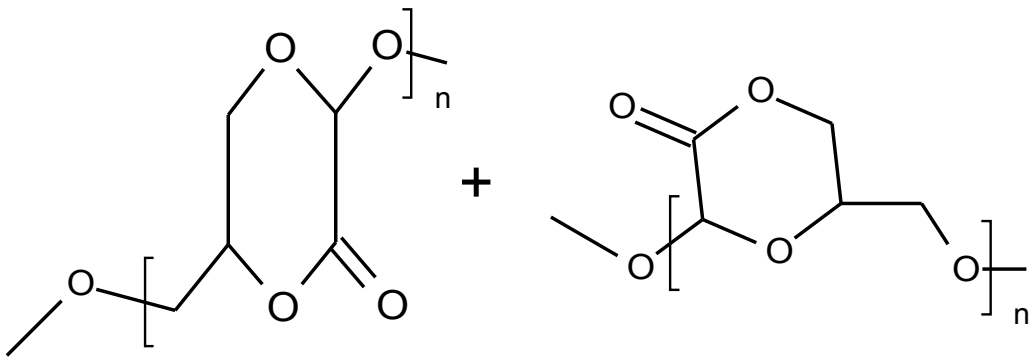


I II

wherein n >1 and the said repeating units are randomly distributed in said polymer chains.

2. The terpolymer of claim 1 wherein n is an integer from 2 to 100.

3. A process for preparing hydrolytically degradable random terpolymers of poly(acetal-lactone-ester) exhibiting said mixture of repeating unit formulas I and II, comprising:



I II

wherein n is as previously described,

a). by mixing glycerol with glyoxylic acid, in essentially equal molar ratios,

b). and under means of heat and vacuum sufficient for removal of water of condensation from the reaction mixture.

4. The process of claim 3, wherein an acid catalyst is added to said reaction mixture at step a, said acid is a protonic mineral acids such as sulfuric, hydrochloric, or p-toluenesulfonic acid, or methanesulfonic acid, and the like and is employed at minimum levels of 0.01-1.0 % of the reaction mixture.

5. The process of claim 3, wherein a thermoplastic polymer is obtained, said uncross-linked polymer is soluble in solvents consisting individually of DMSO, DMF, and NMP.

6. The process of claim 3, wherein the polymerization results in a thermoset polymer, said polymer forms gels in solvents consisting individually of DMSO, DMF, and NMP.

7.The process of claim 3, wherein at said thermoplastic solvent soluble polymer stage, pharmaceutical drug ingredients and excipients are mixed into said polymer, forming soluble, or suspensions of said additives.

8. The process of claim 7, wherein said formulated thermoplastic terpolymer is further reacted with means for heating and evacuating said terpolymer to form said crosslinked thermset polymer.

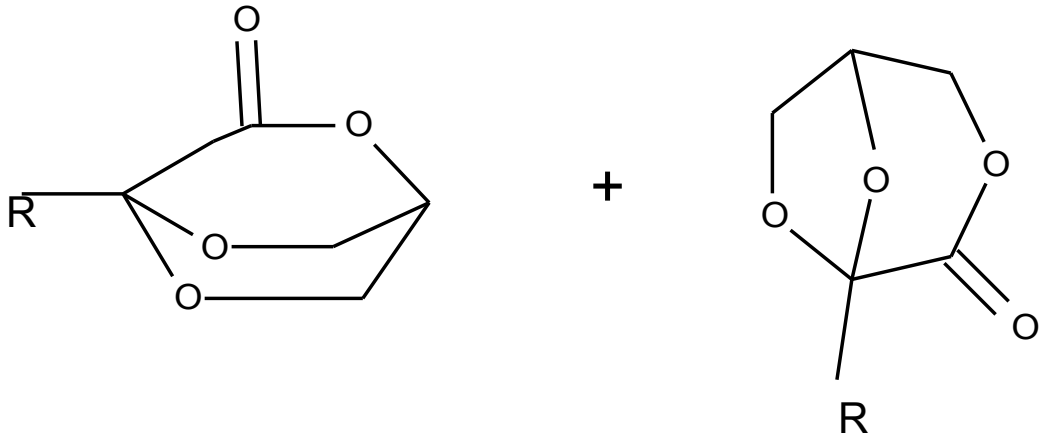
9. The process of claims 7 wherein said formulated terpolymer, when added to aqueous body fluids, dissolves releasing said actives.

10. The process of claim 8 wherein said formulated terpolymer when added to aqueous body fluids, dissolves releasing said actives.

11. The process of claim 7, wherein said thermoplastic polymer is first dissolved in a solvent and then formulated with pharmaceutical active ingredients and necessary excipients.

12 Isomeric compounds having the formulas I and II:

wherein R is the residue of alpha-keto acids.



I II

13. The compounds of claim 12, wherein said compounds are mixtures in the ratio of 50% to 99% of one to the other.

14. The compounds of claim 12, wherein R is hydrogen or methyl.

15. The compounds of claim 12, wherein R is and alkyl group of 2-20 carbon atoms optionally substituted with aromatic, oxygen, sulfur, halogens, and silicone.

16. The above said compounds of claim 12, wherein R is an aromatic compound.

17. A process for synthesizing said bicyclic ketal lactones of claim12, comprising reacting,

    a). said alpha keto-carboxylic acid and glycerol, catalyzed by said acid catalysts,

    b). with means of heating at temperatures of up to 175C and vacuum means such that two equivalents of water of condensation are removed,

    c). and the said bicyclic derivatives are distilled under vacuum means and collected leaving an undistilled residue.

18. The process of claim 16 wherein said undistilled residue is hydrolyzed with water so as to reform said starting alpha keto-carboxylic acid and glycerol in order to then reform said reaction starting compounds which can be again reacted by said reaction and distilled as before under vacuum to generate a new batch of desired said bycyclic compounds.

19. The process of claim 16, wherein the said bicyclic ketal lactones are redistilled in order to obtain purer compounds.

20. The process of claim 16, wherein the said bicyclic ketal lactones are purified by recrystallization.

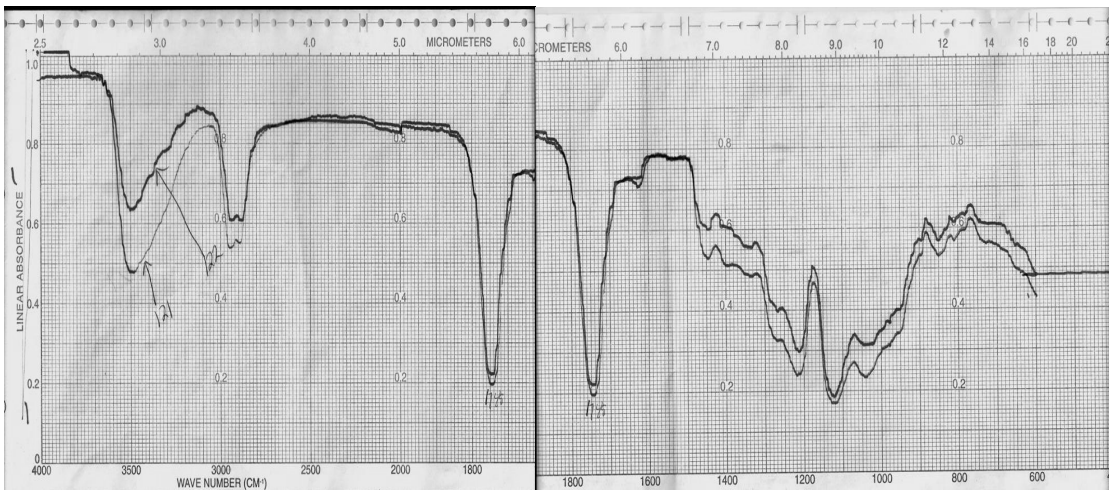


Fig. 3. Infrared spectrum of thermoplastic polymer

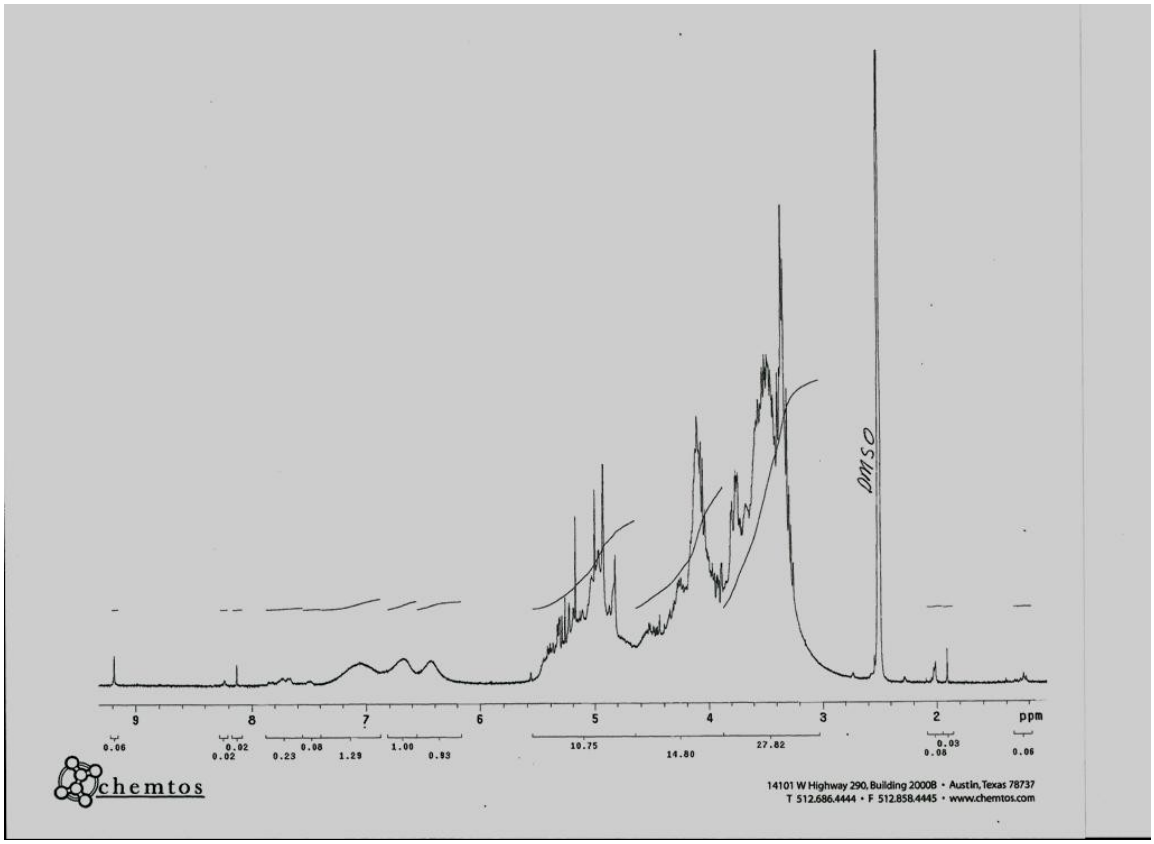


Fig 4. Polymer sample dissolved in d6 DMSO.

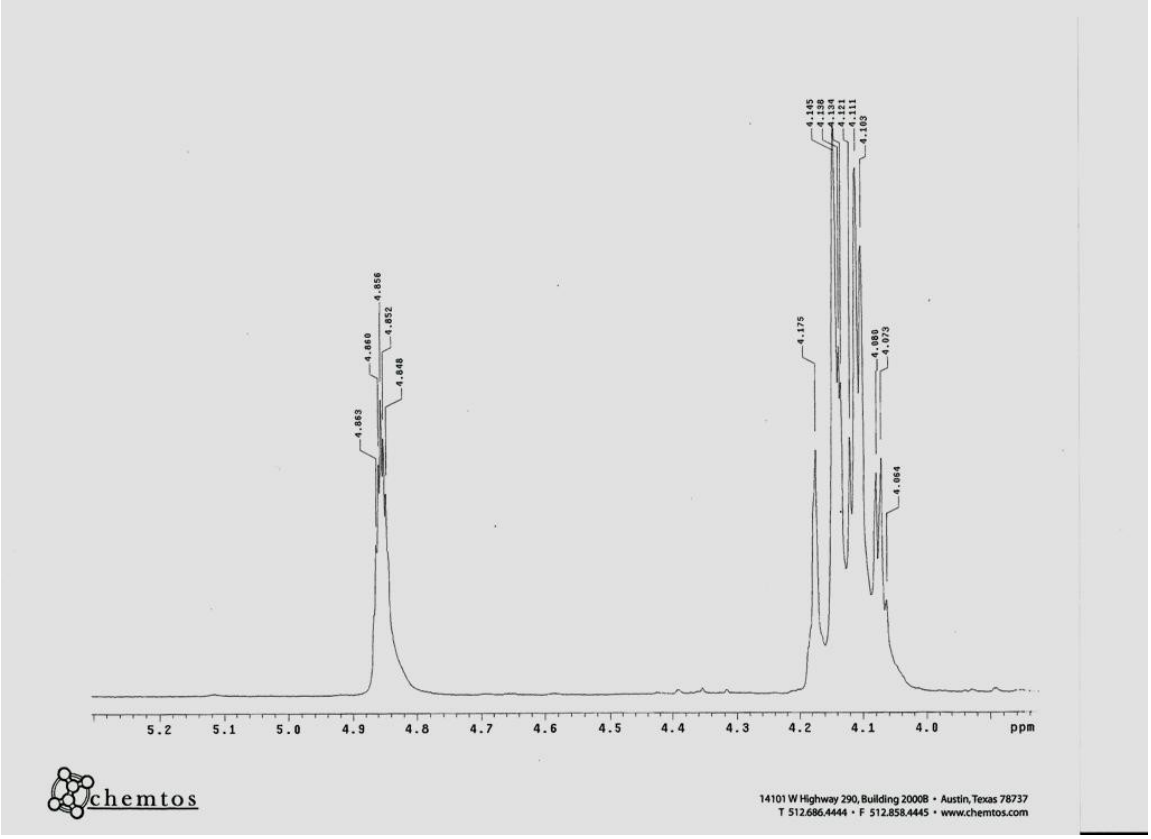


Fig. 5B Greater detail

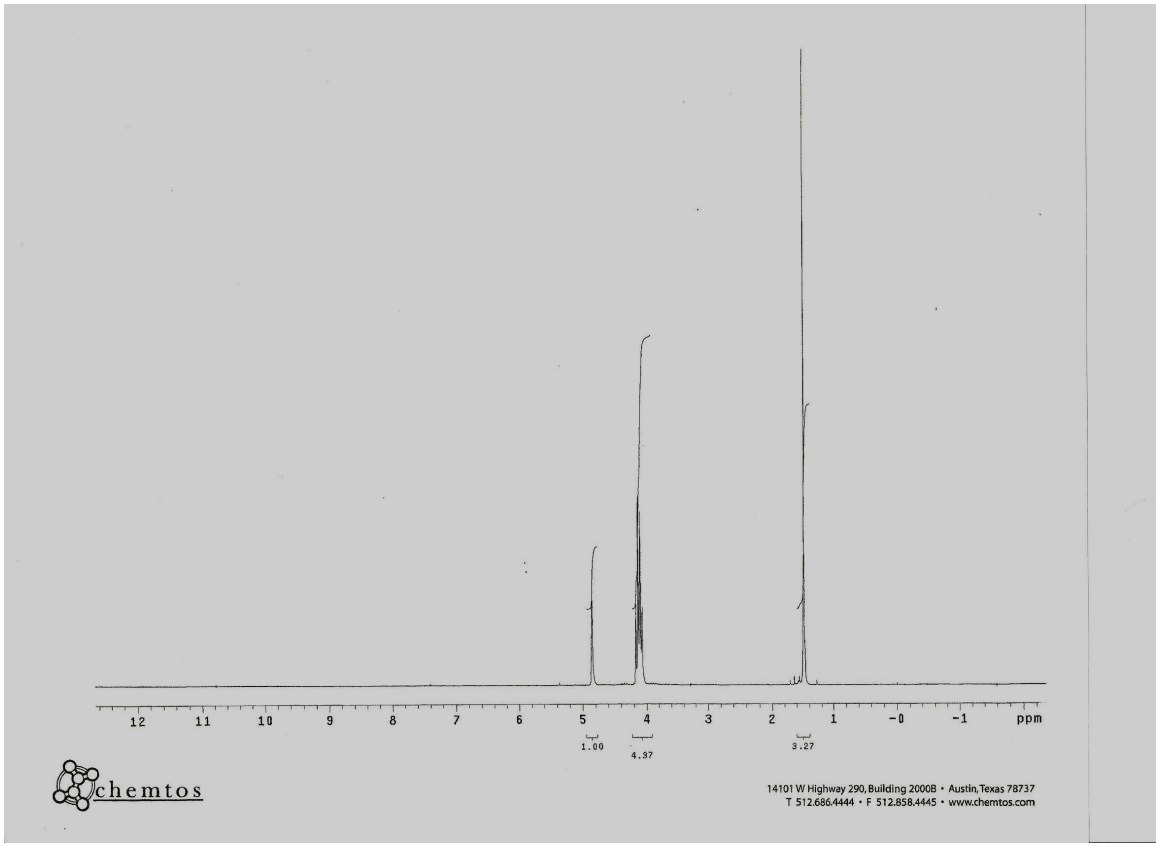


Fig5A. Bicyclic monomer 96% by gc (above more detail).

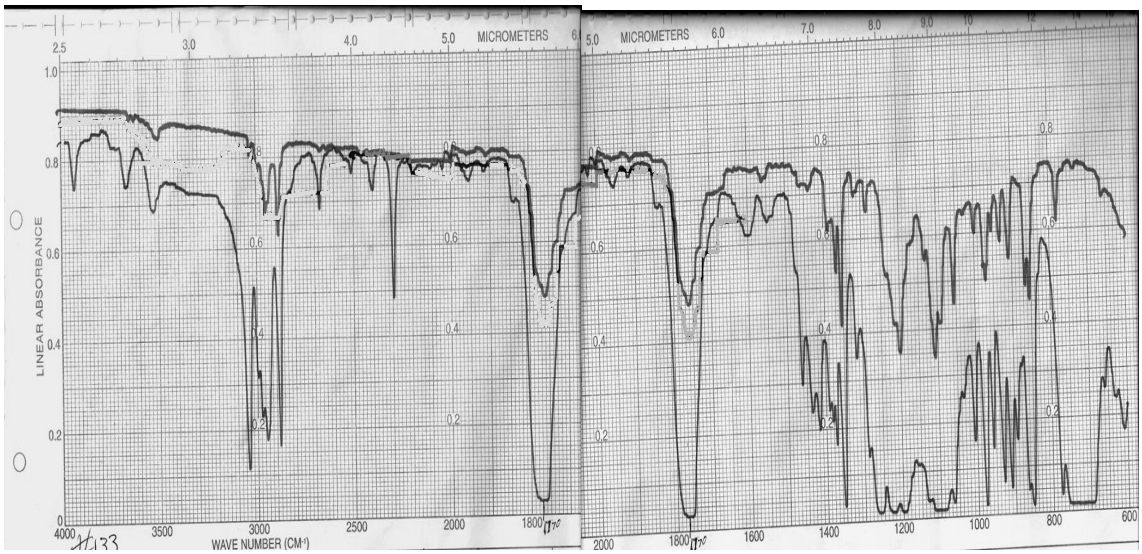


Fig. 6. IR of bicyclic monomer...top spectra is a neat film on salt plates...bottom is a solution in CH2CL2 .