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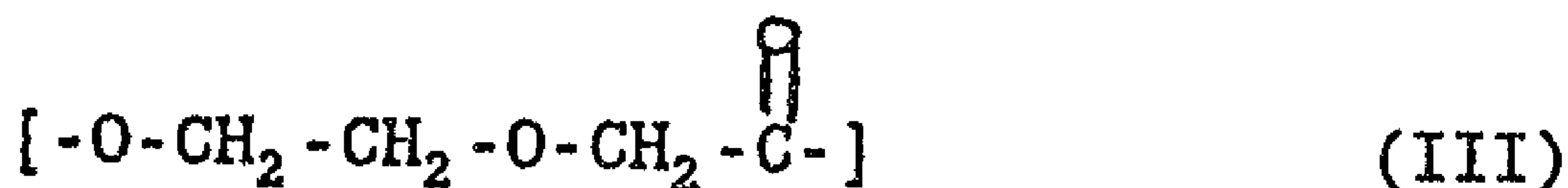
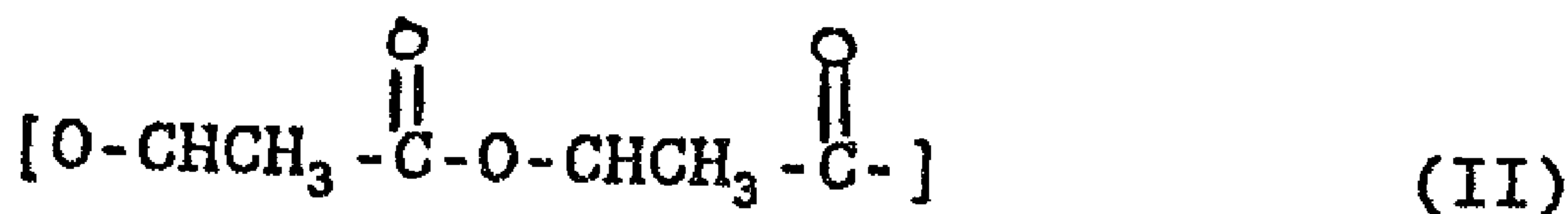
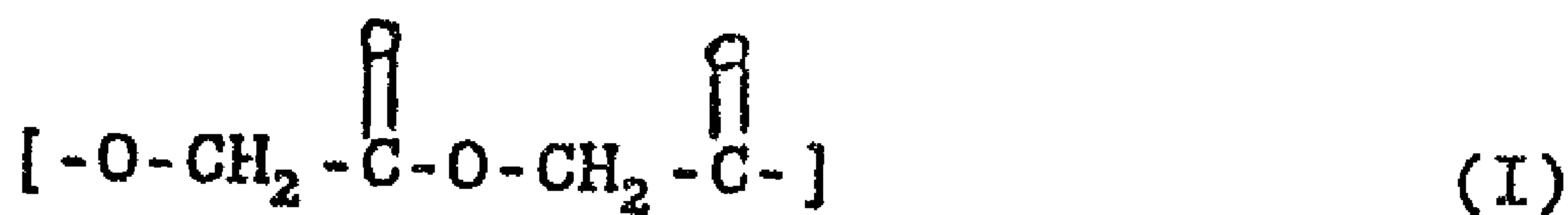
(72) Inventeurs/Inventors:
KENNEDY, JOHN, US;
KAPLAN, DONALD S., US;
MUTH, ROSS R., US

(73) Propriétaire/Owner:
UNITED STATES SURGICAL CORPORATION, US

(74) Agent: MCFADDEN, FINCHAM

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(54) Title: ABSORBABLE COMPOSITION

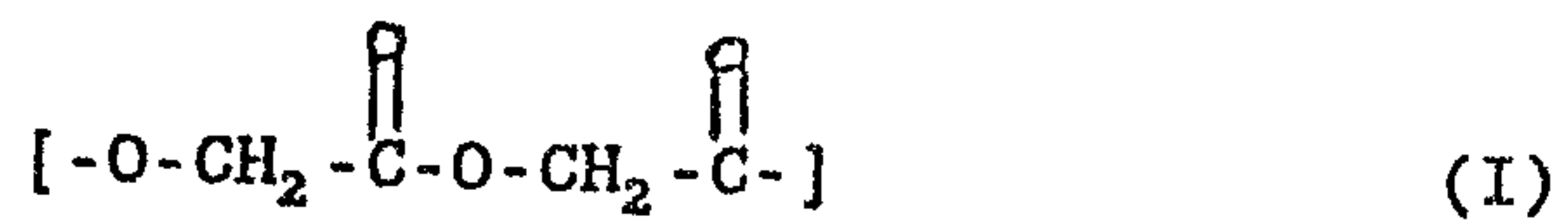


(57) Abrégé/Abstract:

The invention relates to a block copolymer which comprises a proportion of units having the formula: (see formula I) as one of the blocks, and another of the blocks comprising a proportion of units having the formula: (see formula II) and a proportion of units having the formula: (see formula III) the units of formula (II) and formula (III) being randomly combined.

Abstract

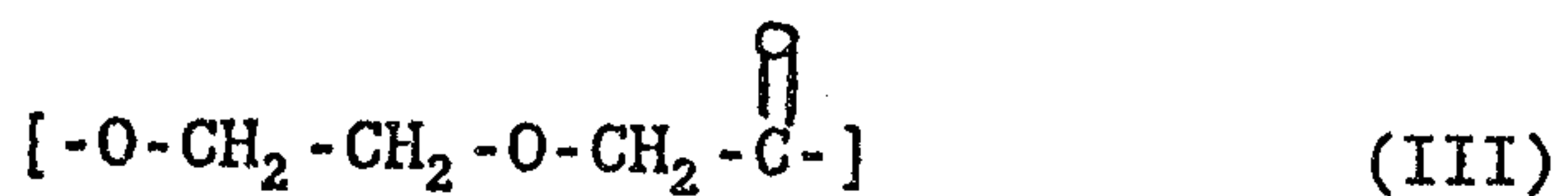
The invention relates to a block copolymer which comprises a proportion of units having the formula:



as one of the blocks, and another of the blocks comprising a proportion of units having the formula:



and a proportion of units having the formula:



the units of formula (II) and formula (III) being randomly combined.

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ABSORBABLE COMPOSITION

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BACKGROUND OF THE INVENTION

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1. Field of the Invention

This invention relates to a copolymer, and more particularly to a surgical article manufactured from the copolymer and to a method of manufacturing the copolymer and surgical article.

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2. Background of the Art

Absorbable synthetic polymer sutures known in the prior art are usually manufactured, sold, and used as multifilament braids. The known absorbable polymers containing a glycolic acid ester linkage seem to be well suited for use in fabricating braided sutures. However, monofilament sutures fabricated from such polymers tend to be relatively stiff, particularly in the larger diameters. Yet, some surgeons prefer the suturing characteristics of a monofilament suture because of its smooth, continuous-surface. Thus, it has been recognized for some years that there is a need in surgery for flexible, absorbable, monofilament sutures which retain a safe and useful proportion of their strength for a relatively long period of time in vivo.

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To be fully useful as an absorbable suture it is essential that a monofilament or multifilament not only be absorbable and flexible but it must also be capable of a relatively long period of in vivo strength retention. An appropriate strength retention target for this type suture is considered to be about 35-70 days in vivo.

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1 U.S. Patent No. 4,429,080 to Casey et al discloses
a triblock copolymer wherein the end blocks comprise
polyglycolide, and the middle block comprises a
glycolide/trimethylene carbonate copolymer.

5 A new polymer has been developed for use in the
fabrication of absorbable monofilament or multifilament
sutures.

SUMMARY OF THE INVENTION

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Provided herein is a block copolymer for use in
the fabrication of bioabsorbable articles; and a method for
making the same. The block copolymer is composed of
glycolide as one block, and lactide/polydioxanone as the
15 other block. The lactide/polydioxanone is first
copolymerized at a first reaction temperature. The reaction
temperature is then increased and glycolide is added to the
reaction mixture. The resulting copolymer can be fabricated
into both monofilament and multifilament absorbable sutures
20 with advantageous flexibility and knot pull characteristics.

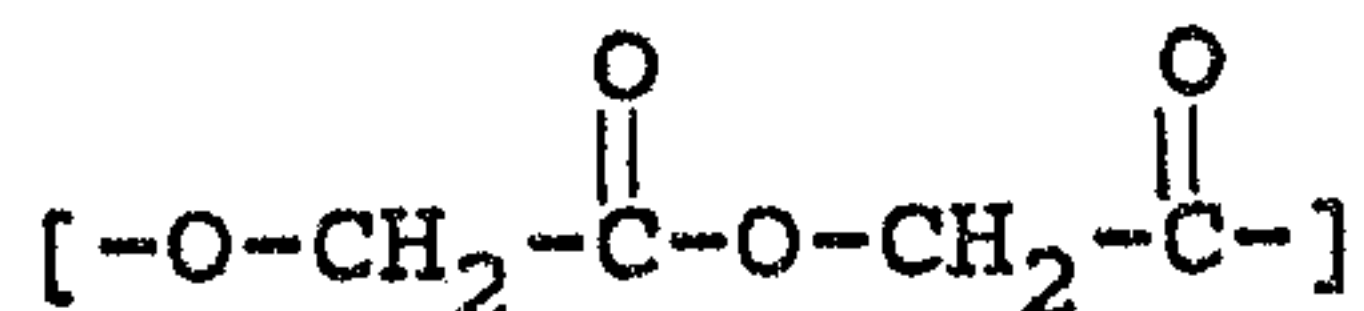
DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Bioabsorbable materials useful for fabricating
25 surgical articles, such as sutures, surgical clips, etc.,
include homopolymers and copolymers of glycolide, lactide,
(both glycolides and lactides are examples of hard phase
forming monomers) 1-4-dioxanone, trimethylene carbonate,
and caprolactone.

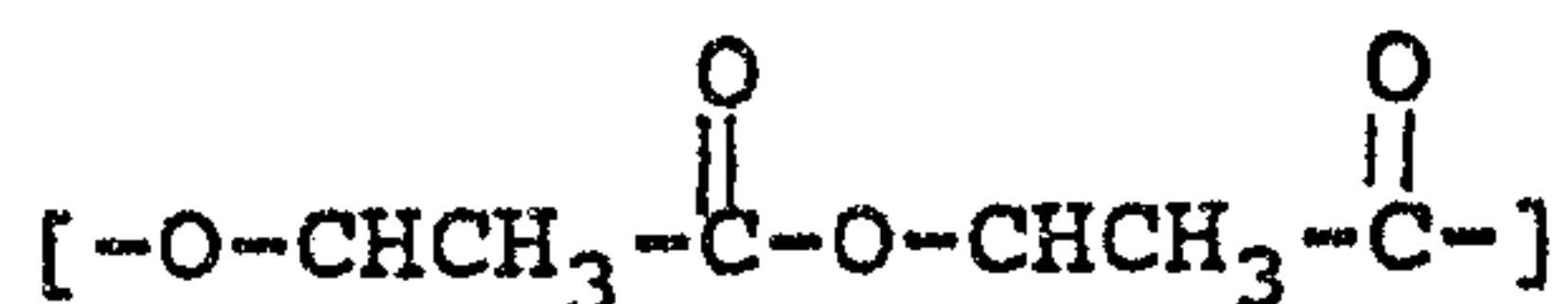
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1 The present invention relates to a block copolymer
having one block composed of units of glycolide:

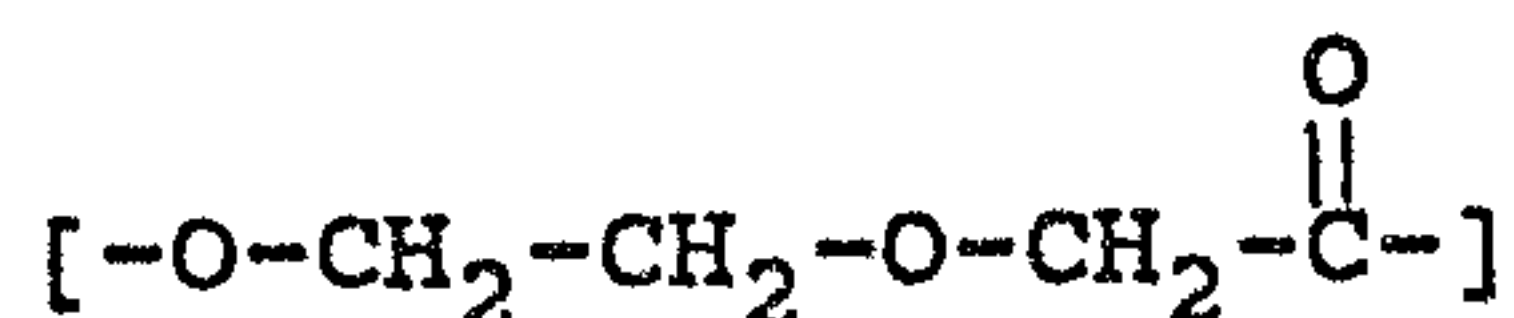


5 and another block composed of units of L-lactide:



copolymerized with randomly intermingled units of 1,4-
dioxanone:

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The block copolymer is preferably a diblock copolymer
prepared by first copolymerizing the lactide monomer with
1,4-dioxanone and then polymerizing that copolymer with
15 glycolide.

Catalysts suitable for carrying out the
polymerization include compounds of tin, aluminum, antimony,
lead, boron, and titanium. A preferred catalyst is stannous
octoate. Other catalysts include stannous chloride, dibutyl
20 tin dilaurate, dibutyl tin diacetate, dibutyl tin
dichloride, stannic chloride pentahydrate, aluminum
isopropoxide, antimony trioxide, stannic fluoride, stannous
citrate, stannous acetate, antimony trifluoride, tin
tetraisopropoxide, lead oxide, tetraisopropyl titanate,
25 titanium acetyl acetonate, tetraoctylene glycol titanate,
boron trifluoride etherate, and aluminum trichloride.

The preferred composition range of the monomer
units of the block copolymer in terms of weight % of the
final block copolymer is set forth below in Table 1.

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TABLE 1

Block Copolymer Composition
(weight per cent)

5	<u>Monomer unit</u>	<u>Broad Range</u>	<u>Preferred Range</u>
	glycolide	55% to 85%	65% to 75%
	lactide	1% to 20%	3% to 8%
	1,4-dioxanone	10% to 40%	20% to 30%

10 In the examples below a preferred composition of the block copolymer of the present invention includes 70 wt% of glycolide, 25.5 wt.% 1,4-dioxanone, and 4.5 wt.% lactide.

The polymerization reaction may be carried out at a temperature of from 100°C to 250°C. The first step is the
 15 polymerization of the lactide and 1,4-dioxanone, which is carried out at a temperature of between about 100°C and 150°C and preferably about 120°C. This reaction temperature is maintained until the polymerization is substantially completed, i.e., about 30 minutes.

20 The second step comprises raising the reaction temperature to between about 200°C and 250°C, and adding glycolide preferably when the temperature has reached about 200°C. The glycolide will then copolymerize with the lactide/dioxanone copolymer to create a separate block in a
 25 diblock copolymer.

The resulting copolymer may then be subjected to further processing such as extruding, drawing, relaxing, etc.

30 The preferred area for use of the present invention is in the fabrication of sterile synthetic absorbable surgical articles, specifically sutures, wherein

1 glycolide is employed as the predominant monomer. The
sutures may be either multifilament or monofilament.
Absorbable monofilament sutures fabricated from such
copolymers have been found to be useful in that they are
5 more flexible and more resistant to in vivo strength loss
than corresponding size monofilament sutures fabricated from
a polymer containing only glycolic acid ester linkage.

The surgical articles are fabricated from the
copolymer using conventionally employed forming procedures,
10 such as extrusion, and subsequently sterilized. The
resulting surgical articles are employed in a conventional
manner.

Surgical sutures fabricated from the polymer of
the present invention display good flexibility and knot pull
15 strength.

The following examples illustrate procedures which
are useful in conjunction with the practice of the present
invention but are not to be taken as being limiting thereto.

20

EXAMPLE 1

A conventional polymerization reactor was
preheated to a temperature of 120°C. Quantities of 510
grams of 1,4-dioxanone, and 90 grams of L-lactide were added
to the reactor with 0.2 grams of stannous octoate catalyst.
25 The reactor was held at 120°C. for 60 hours until
copolymerization was substantially completed. A sample of
the polymer, designated as Sample 1, was taken at this
point. Then the reactor temperature was gradually
increased. When the reactor temperature reached 180°C,
30 Sample 2 was taken of the polymer. When the temperature
reached 200°C, 1400 grams of glycolide was added to create a

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1 block copolymer having at least one glycolide block and at
 least one lactide/dioxanone block. When the reactor
 temperature reached 220°C the polymer was stirred for 10
 minutes. The polymer was then extruded and Sample 3 was
 5 taken. Samples 1, 2, and 3 were tested for inherent
 viscosity (dl/g), and enthalpy change (ΔH) in calories/gram.

The enthalpy was measured on a differential
 scanning calorimeter which measured the specific heat of the
 sample over a range of temperatures with a scan rate of
 10 20°C/min. The change in enthalpy is an indication of the
 extent of crystallinity.

The inherent viscosity of a polymer is an
 indicator of its molecular weight, and was measured for the
 above-mentioned samples in accordance with standard
 15 measuring techniques and equipment known to those skilled in
 the art.

Table 2 below sets forth inherent viscosity and
 enthalpy data for samples 1, 2, and 3.

20

TABLE 2

<u>Sample</u>	<u>Inherent Viscosity</u>	<u>Enthalpy (ΔH)</u>
1	0.61	11.1 @ 59°C
2	0.61	10.63 @ 332°C
3	0.90	14.99 @ 211°C

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1 The above data indicate that sample 3, which was
taken from the polymer after the glycolide was copolymerized
with the lactide/dioxanone copolymer, exhibited a higher
inherent viscosity and, therefore, a higher molecular
5 weight. This indicates copolymerization of the glycolide
occurred. Also shown is a greater ΔH , which indicates a
greater degree of crystallinity. These physical properties,
i.e., higher molecular weight and greater crystallinity,
indicate that the material is suitable for fabrication into
10 a fiber.

EXAMPLE 2

The block copolymer of Example 1 was extruded,
ground and dried at from 20 to 120°C at a pressure of less
15 than 10 torr. The resulting material was then formed by
extrusion into a monofilament with an Instron rheometer
(Dc=0.0301"; Lc=1.001") at a temperature of 203°C. The
extrusion speed was 3 inches per minute. The monofilament
was then dried at room temperature overnight. The
20 monofilament was then drawn at a 4.5x draw ratio in an oven
at 60°C by being passed around two godgets. The first
godget providing a linear tangential velocity of 10 feet per
minute and the second godget providing a linear tangential
velocity of 45 feet per minute.

25 The drawn monofilament was then tested for
straight pull and knot pull strength. An Instron Series 1X
Automated Materials Testing System v4.03e was employed with
the following parameters and conditions: Interface type
1011 series; Sample rate = 20.00 pts/sec.; crosshead speed =
30 2.0 inches/min.; humidity = 50%; temperature = 73°F.

1 Specimens of the monofilament were tested and the results of the testing are set forth below in Table 3.

5

TABLE 3
(Specimen diameter = 0.0073 inches/0.1854 mm)

	<u>STRAIGHT PULL</u>	<u>KNOT-PULL</u>
Avg. load @ maximum load (lbs.)	3.111	2.780
10 Avg. Elongation at maximum load %	27.59	22.470
Avg. Young's Modulus (kpsi)	541.8	----

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EXAMPLE 3

The filament of Example 2 was then subjected to controlled shrinkage or relaxation in accordance with the following method.

20

The monofilament was placed in a hot air oven at a temperature of 75°C for 10 minutes. The length of the filament before treatment was 91.8cm. After treatment, the filament length was 82.6cm. Thus, the observed shrinkage was 10%.

25

After relaxation, the filament was tested for inherent viscosity and mechanical properties in accordance with the methods as described in Examples 1 and 2. The results of the testing are set forth below in Table 4.

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TABLE 4

Post shrinkage data

	Inherent viscosity	0.79/0.82
5	Diameter	0.209mm (.00823 inches)
	Avg. load at maximum load (knot pull)	1.24 kg (2.728 lbs.)
10	Avg. load at maximum load (straight pull)	1.45 kg (3.20 lbs.)
	Elongation at maximum load (straight pull)	39%
15	Young's Modulus (straight pull)	513.2 kpsi

20 The data of the above examples indicate that the copolymer of the present invention is advantageous for the manufacture of a monofilament suture. The block copolymer described above is bioabsorbable and, as seen from the Young's modulus value, is flexible, strong, and possesses advantageous handling characteristics.

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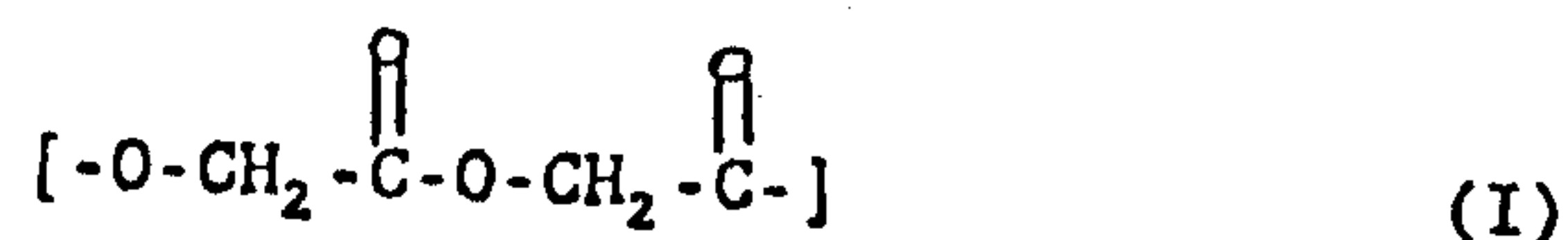
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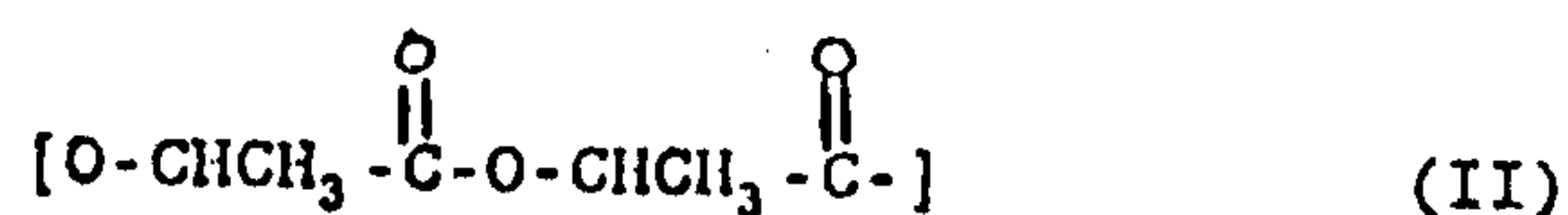
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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

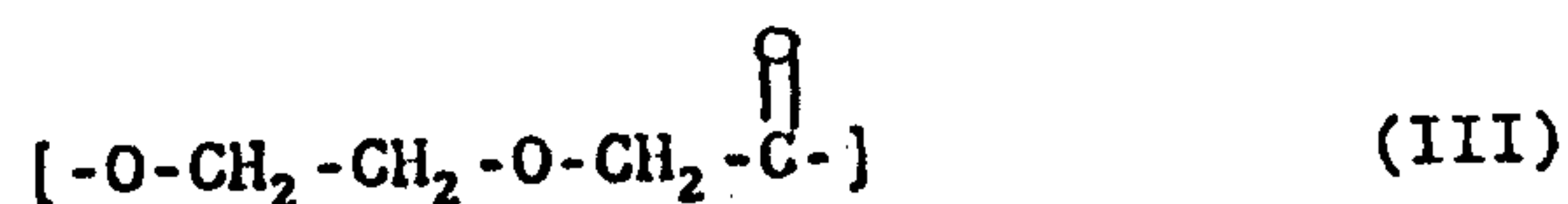
1. A block copolymer which comprises a proportion of units having the formula:



as one of said blocks, and another of said blocks comprising a proportion of units having the formula:

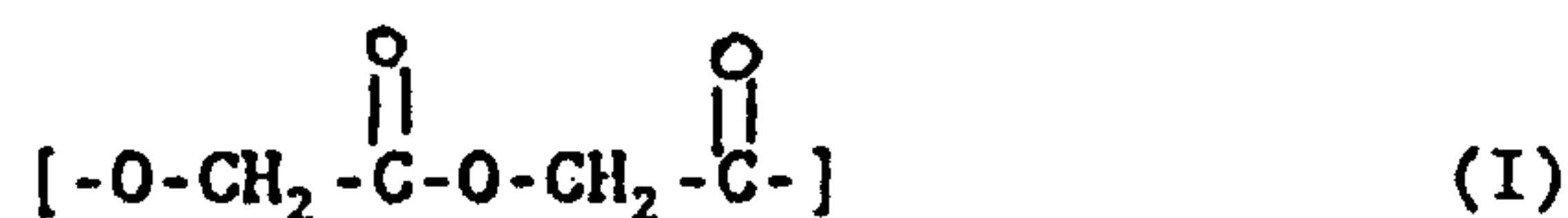


and a proportion of units having the formula:



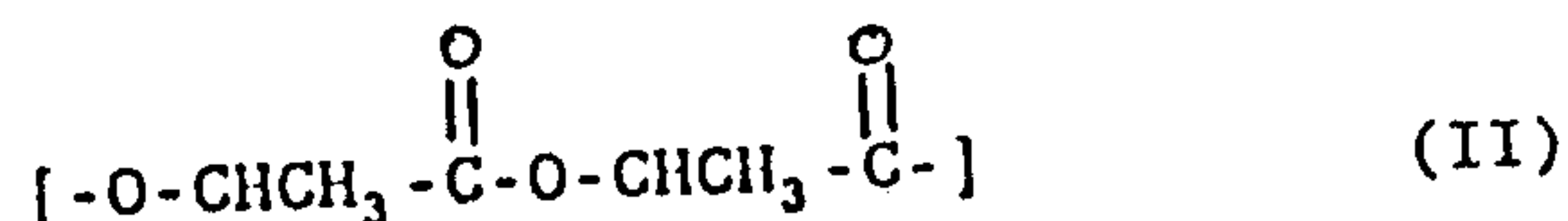
said units of formula (II) and formula (III) being randomly combined.

2. The block copolymer of claim 1, wherein said block copolymer is a diblock copolymer.
3. The block copolymer of claim 1 or 2, wherein from about 55 weight % to about 85 weight % of the block copolymer comprises units of formula (I), from about 1 weight % to about 20 weight % of the block copolymer comprises units of formula (II), and from about 10 weight % to about 40 weight % of the block copolymer comprises units of formula (III).
4. A surgical article manufactured from a block copolymer which comprises a proportion of units having the formula:

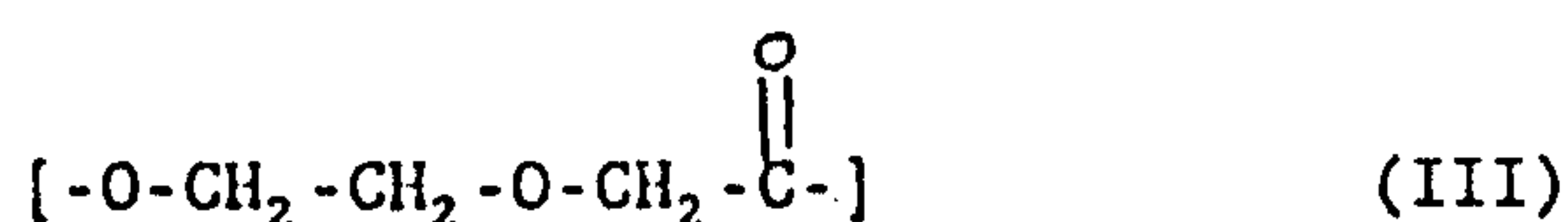


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as one of said blocks, and another of said blocks comprising a proportion of units having the formula:



and a proportion of units having the formula:



said units of formula (II) and formula (III) being randomly combined.

5. The surgical article of claim 4, wherein said block copolymer is a diblock copolymer.
6. The surgical article of claim 4 or 5, wherein said surgical article is a suture.
7. The surgical article of claim 6, wherein said suture is a monofilament suture.
8. The surgical article of any one of claims 4 to 7, wherein from about 55 weight % to about 85 weight % of the block copolymer comprises units of formula (I), and from about 1 weight % to about 20 weight % of the block copolymer comprises units of formula (II), and from about 10 weight % to about 40 weight % of the block copolymer comprises units of formula (III).
9. A method for preparing a bioabsorbable block copolymer, comprising:
 - (a) polymerizing a mixture of lactide and 1,4-dioxanone at a first reaction temperature to create a copolymer thereof;
 - (b) polymerizing glycolide with the lactide/1,4-dioxanone copolymer of

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step (a) at a second reaction temperature to create the bioabsorbable block copolymer.

10. The method of claim 9, wherein said first reaction temperature comprises a temperature of from about 100°C to about 150°C.
11. The method of claim 9 or 10, wherein said second reaction temperature comprises a temperature of from about 200°C to about 250°C.
12. The method of any one of claims 9 to 11, wherein step (a) is carried out in the presence of a polymerization catalyst.
13. The method of claim 12, wherein said catalyst is selected from the group consisting of stannous chloride, dibutyl tin dilaurate, dibutyl tin diacetate, dibutyl tin dichloride, stannic chloride pentahydrate, aluminum isopropoxide, antimony trioxide, stannic fluoride, stannous citrate, stannous acetate, antimony trifluoride, tin tetraisopropoxide, lead oxide, tetraisopropyl titanate, titanium acetyl acetonate, tetraoctylene glycol titanate, boron trifluoride etherate, and aluminum trichloride.
14. A method for making a bioabsorbable surgical article, comprising:
 - (a) polymerizing a mixture of lactide and 1,4-dioxanone at a first reaction temperature to create a copolymer thereof;
 - (b) polymerizing glycolide with the lactide/1,4-dioxanone copolymer of step (a) at a second reaction temperature to create a bioabsorbable block copolymer;
 - (c) forming said block copolymer.

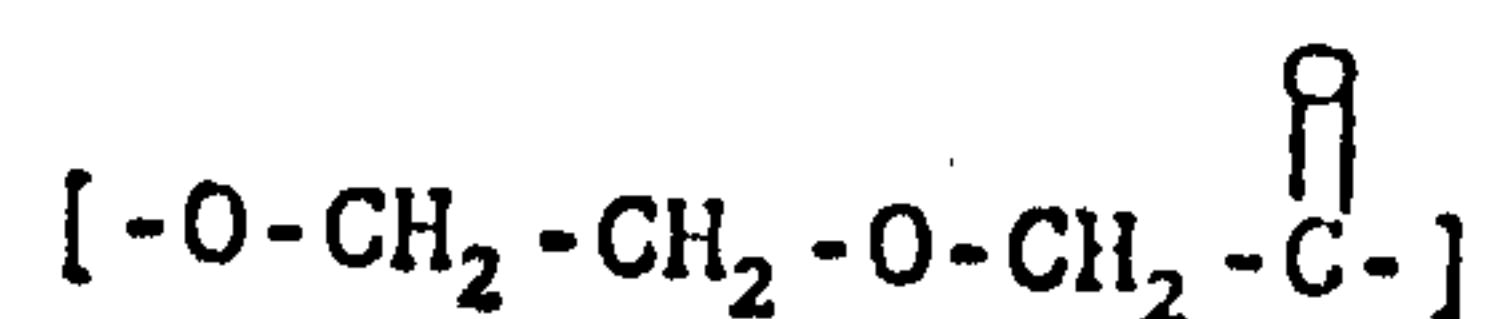
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15. The method of claim 14, wherein said forming includes the step of extruding the block copolymer into a filament.
16. The method of claim 14 or 15, wherein the bioabsorbable surgical article comprises a suture.
17. The method of any one of claims 14 to 16, wherein said first reaction temperature comprises a temperature of from about 100°C to about 150°C.
18. The method of any one of claims 14 to 17, wherein said second reaction temperature comprises a temperature of from about 200°C to about 250°C.
19. The method of any one of claims 14 to 18, wherein step (a) is carried out in the presence of a polymerization catalyst.
20. The method of any one of claims 14 to 19, wherein from about 55 weight % to about 85 weight % of the block copolymer comprises units derived from glycolide, from about 1 weight % to about 20 weight % of the block copolymer comprises units derived from lactide and from about 10 weight % to about 40 weight % of the block copolymer comprises units derived from 1,4-dioxanone.
21. The method of claim 16, additionally comprising drawing the suture and relaxing the suture.
22. The method of any one of claims 14 to 21, wherein said block copolymer is a diblock copolymer.
23. The method of claim 19, wherein said catalyst is stannous octoate.
24. The method of claim 19, wherein said catalyst is selected from the group

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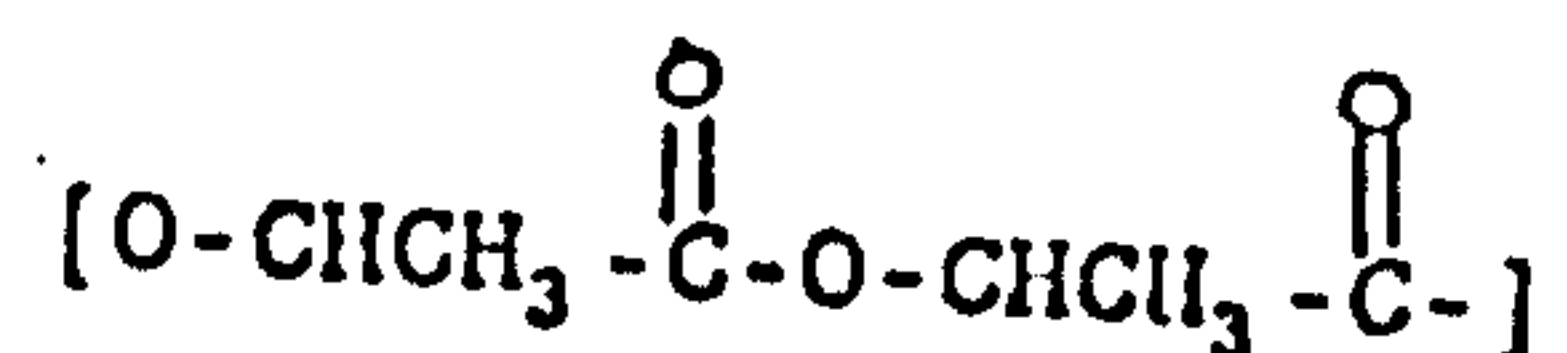
consisting of stannous chloride, dibutyl tin dilaurate, dibutyl tin diacetate, dibutyl tin dichloride, stannic chloride pentahydrate, aluminum isopropoxide, antimony trioxide, stannic fluoride, stannous citrate, stannous acetate, antimony trifluoride, tin tetraisopropoxide, lead oxide, tetraisopropyl titanate, titanium acetyl acetonate, tetraoctylene glycol titanate, boron trifluoride etherate, and aluminum trichloride.

25. A block copolymer which comprises a proportion of units of one or more hard phase forming monomers as one of said blocks, and another of said blocks comprising a proportion of units having the formula:



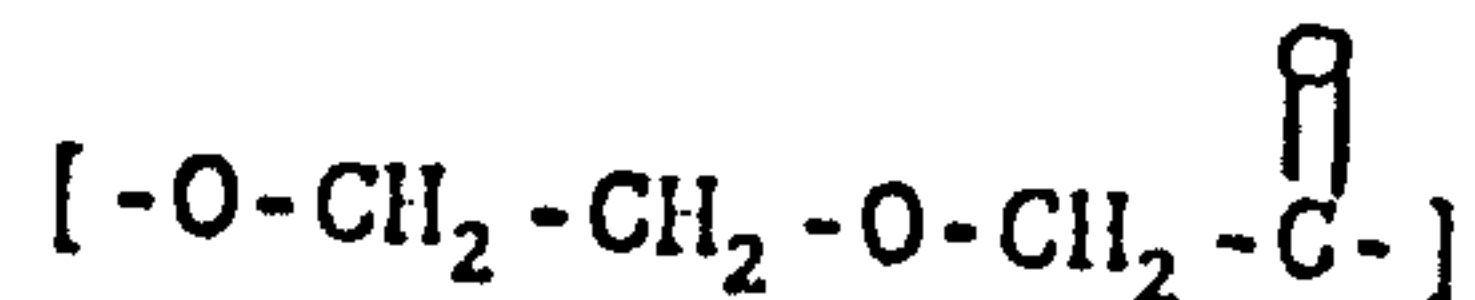
randomly combined with a proportion of units of one or more hard phase forming monomers, said hard phase forming monomers selected from the group consisting of glycolide, lactide and mixtures thereof.

26. The block copolymer of claim 25, wherein said block copolymer is a diblock copolymer.
27. The block copolymer of any one of claims 25 to 26, wherein from about 1 weight % to about 20 weight % of the block copolymer comprises units having the formula:

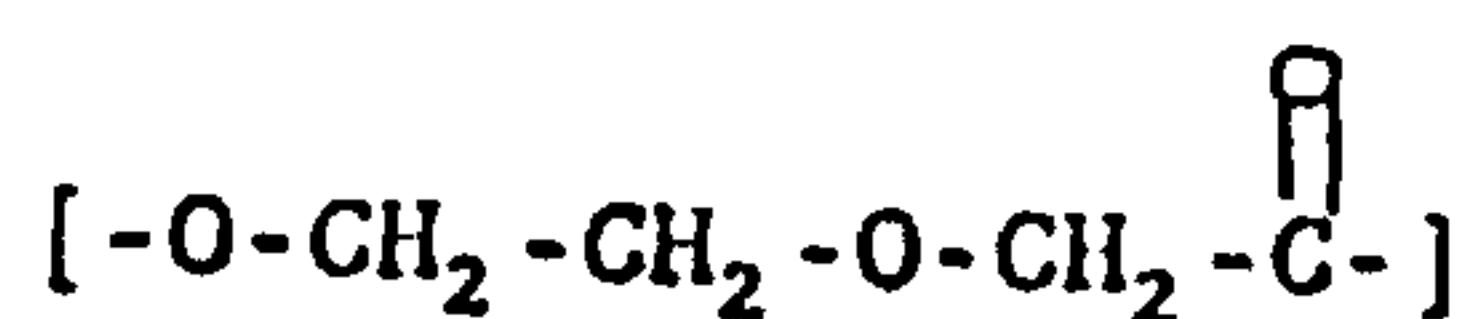


28. The block copolymer of any one of claims 25 to 26, wherein the hard phase forming monomers comprise about 10 weight % to about 40 weight % of the block containing units of formula:

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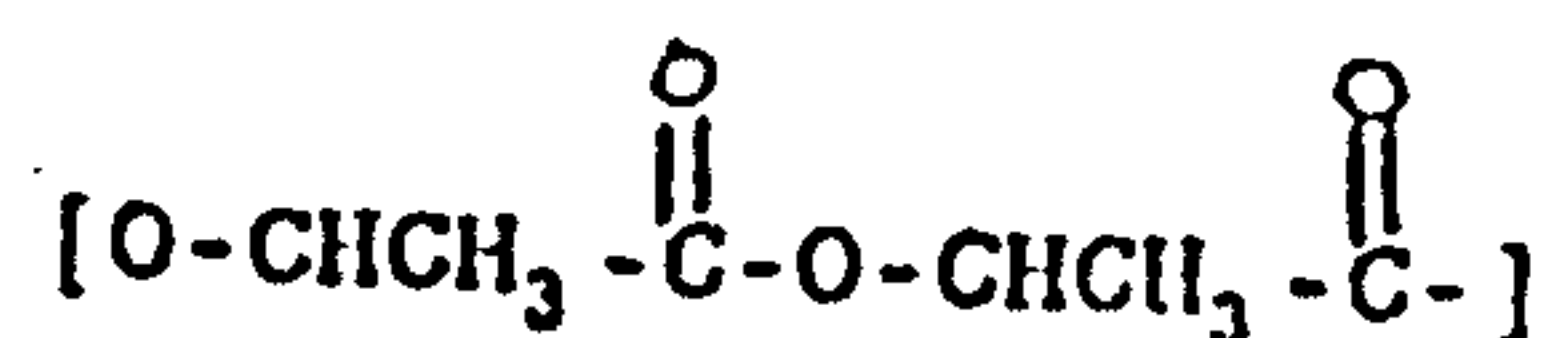


29. A surgical article manufactured from a block copolymer which comprises a proportion of units of one or more hard phase forming monomers as one of said blocks, and another of said blocks comprising a proportion of units having the formula:



randomly combined with a proportion of units of one or more hard phase forming monomers, said hard phase forming monomers selected from the group consisting of glycolide, lactide and mixtures thereof.

30. The surgical article of claim 29, wherein said block copolymer is a diblock copolymer.
31. The surgical article of claim 29 or 30, wherein said surgical article is a suture.
32. The surgical article of claim 31, wherein said suture is a monofilament suture.
33. The surgical article of any one of claims 29 to 32, wherein from about 1 weight % to about 20 weight % of the block copolymer comprises units having the formula:



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34. A method for preparing a bioabsorbable block copolymer, comprising:
- (a) polymerizing a mixture of one or more hard phase forming monomers and 1,4-dioxan-2-one at a first reaction temperature to create a copolymer thereof;
- (b) polymerizing one or more hard phase forming monomers with the copolymer of step (a) at a second reaction temperature to create the bioabsorbable block copolymer,
- wherein said hard phase forming monomers are selected from the group consisting of glycolide, lactide and mixtures thereof.
35. The method of claim 34, wherein said block copolymer is a diblock copolymer.
36. The method of claim 34 or 35, wherein said first reaction temperature comprises a temperature of from about 100°C to about 150°C.
37. The method of any one of claims 34 to 36, wherein said second reaction temperature comprises a temperature of from about 200°C to about 250°C.
38. The method of any one of claims 34 to 37, wherein step (a) is carried out in the presence of a polymerization catalyst.
39. The method of claim 38, wherein said catalyst is stannous octoate.
40. The method of claim 38, wherein said catalyst is selected from the group consisting of stannous chloride, dibutyl tin dilaurate, dibutyl tin diacetate, dibutyl tin dichloride, stannic chloride pentahydrate, aluminum isopropoxide, antimony trioxide, stannic fluoride, stannous citrate, stannous acetate, antimony trifluoride, tin tetraisopropoxide, lead oxide, tetraisopropyl titanate, titanium acetyl acetonate, tetraoctylene glycol titanate, boron trifluoride etherate, and aluminum trichloride.

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41. A method for making a bioabsorbable surgical article, comprising:
- (a) polymerizing a mixture of one or more hard phase forming monomers and 1,4-dioxan-2-one at a first reaction temperature to create a copolymer thereof;
 - (b) polymerizing one or more hard phase forming monomers with the copolymer of step (a) at a second reaction temperature to create a bioabsorbable block copolymer;
 - (c) forming a surgical article from said block copolymer;
- wherein said hard phase forming monomers are selected from the group consisting of glycolide, lactide and mixtures thereof.
42. The method of claim 41, wherein said forming includes the step of extruding the block copolymer into a filament.
43. The method of claim 41 or 42, wherein the bioabsorbable surgical article comprises a suture.
44. The method of claim 43, additionally comprising drawing the suture and relaxing the suture.
45. The method of any one of claims 41 to 44, wherein said block copolymer is a diblock copolymer.
46. The method of any one of claims 41 to 45, wherein said first reaction temperature comprises a temperature of from about 100°C to about 150°C.
47. The method of any one of claim 41 to 46, wherein said second reaction temperature comprises a temperature of from about 200°C to about 250°C.

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48. The method of any one of claims 41 to 47, wherein step (a) is carried out in the presence of a polymerization catalyst.
49. The method of claim 48, wherein the catalyst is stannous octoate.
50. The method of claim 48, wherein said catalyst is selected from the group consisting of stannous chloride, dibutyl tin dilaurate, dibutyl tin diacetate, dibutyl tin dichloride, stannic chloride pentahydrate, aluminum isopropoxide, antimony trioxide, stannic fluoride, stannous citrate, stannous acetate, antimony trifluoride, tin tetraisopropoxide, lead oxide, tetraisopropyl titanate, titanium acetyl acetonate, tetraoctylene glycol titanate, boron trifluoride etherate, and aluminum trichloride.
51. The method of any one of claims 41 to 50, wherein from about 55 weight % to about 85 weight % of the block copolymer comprises units derived from glycolide.
52. The method of any one of claims 41 to 50, wherein from about 1 weight % to about 20 weight % of the block copolymer comprises units derived from lactide.
53. The method of any one of claims 41 to 50, wherein from about 10 weight % to about 40 weight % of the block copolymer comprises units derived from 1,4-dioxan-2-one.

