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(54) Title: POLYMERIZATION OF LACTIDE WITH RARE-EARTH METAL CATALYSTS

(57) Abstract

A process for polymerizing lactide and up to 20 mole percent of another lactone in the absence of solvent at 100 to 220 °C using an yttrium or lanthanide series rare earth metal compound of the general formula MZ_3 as catalyst, wherein M is the metal and at least one Z is $-OCR_3$, where R is independently hydrogen, hydrocarbyl or substituted hydrocarbyl.

TITLE

POLYMERIZATION OF LACTIDE WITH RARE-EARTH METAL CATALYSTS.

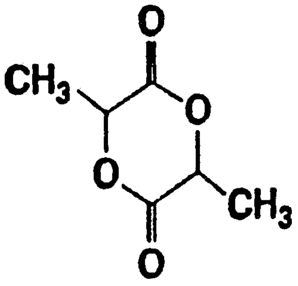
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the polymerization of molten lactide (either S or R) using an yttrium or lanthanide series rare earth metal based catalyst.

2. Description of the Related Art

Lactides are presently polymerized to high molecular weight plastics using stannous 2-ethylhexanoate (tin octanoate) as the catalyst by ring opening polymerization of the cyclic ester:

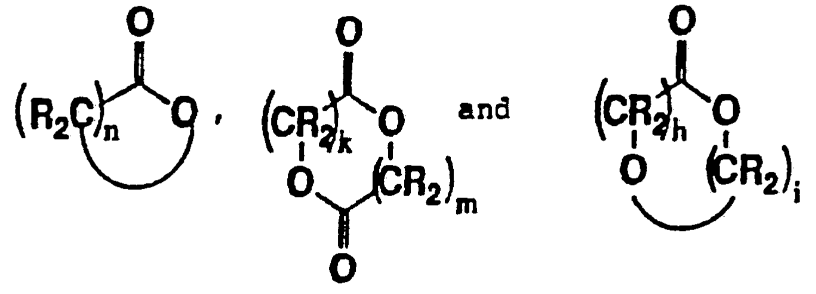


These polymers of lactide are useful in medical applications such as wound closure devices, orthopedic implants, and controlled release drug carriers.

U.S. Patent 5,028,667 discloses the polymerization of various lactones including lactide using yttrium and lanthanide series rare earth based catalysts.

SUMMARY OF THE INVENTION

The present process relates to a process for the polymerization of lactide and optionally up to 20 mole % based on lactide of one or more lactones selected from

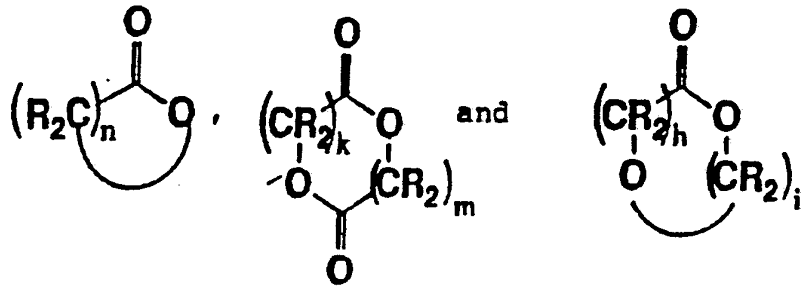


by contacting a melt of lactide and the optional lactone with one or more catalysts having the formula MZ_3, wherein n is 4 or 5, h, i, k and m are independently 1 or 2, each R is independently selected from hydrogen or hydrocarbyl containing up to 20 carbon atoms or substituted hydrocarbyl containing up to 20 carbon atoms, M is chosen from yttrium or a lanthanide series rare earth metal, and Z is $-OCR'_3$ where R′ is independently chosen from hydrogen, hydrocarbyl and substituted hydrocarbyl. Optionally up to two Zs may be other herein below defined materials.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the ring opening polymerization of molten lactide and up to 20 mole % based on lactide of another lactone using as catalysts certain compounds of yttrium or lanthanide series rare earth metal.

The lactones which can be used as comonomers in the process of the present invention include:



wherein n is 4 or 5, h, i, k and m are independently one or two and each R is independently chosen from H or hydrocarbyl containing up to 12 carbon atoms. Preferred lactones are those in which R is hydrogen or methyl, and especially preferred lactones are epsilon-caprolactone, delta-valerolactone, glycolide (1,4-dioxan-2,5-dione), 1,5-dioxepan-2-one and 1,4-dioxan-2-one.

The catalysts, characterized by the formula MZ_3, for this polymerization are compounds of yttrium and the rare earth metals. Rare earth metals include those elements with atomic numbers 57 through 71, namely lanthanum, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, and lutetium. Preferred metals are yttrium, lanthanum, cerium, samarium and dysprosium. Especially preferred is lanthanum and mixtures of yttrium and rare earth metals that are obtained from the mining or smelting of rare earth metal ores. In all of the catalysts the yttrium and rare earth metal are trivalent. The catalyst preferably is at least slightly soluble in the molten lactide.

The group denoted Z bonded to the metal, M, is $-OCR'_3$ where each -R′ is independently chosen from hydrogen, hydrocarbyl of up to 50 carbon atoms and substituted hydrocarbyl of up to 50 carbon atoms. It is to be understood that in the group $-OCR'_3$ the carbon atom bound to the oxygen may be part of a non-aromatic carbocycle or non-aromatic heterocycle formed from that carbon and two of the -R′ groups. Preferred Z groups contain less than 50 carbon atoms and include isopropoxy, 2-ethoxyethoxy and 2-(N,N-dimethylamino)ethoxy.

It is understood that all of the above named Z groups bonded to yttrium or a rare earth metal can initiate polymerization, so that for each mole of catalyst MZ_3 present, up to three polymer chains can be produced.

In contrast to solution polymerizations disclosed in U.S. Patent 5,028,667, we have found such catalysts to give incomplete reaction in the melt polymerization. Surprisingly, certain highly coordinating ligands such as 2,2,6,6-tetramethylheptane-3,5-dionate and acetylacetonate stabilize the catalysts, allowing complete conversion to high molecular weight polymer. Other highly coordinating ligands include fluoride, chloride, bromide, iodide, carboxylate, tetrasubstituted porphyrinato (-2), phthalcyanato (-2), beta keto ester anions such as methyl acetoacetate, dialkylmalonate ion, cyclopentadienide, pentamethylcyclopentadienide, and aryloxide such as phenoxide.

For use herein it is preferred that one Z is an active catalyst group such as $-OCH(CH_3)_2$, $-OCH_2CH_2OCH_2CH_3$ or $-OCH_2CH_2N(CH_3)_2$ and two Z groups are highly coordinating ligands, preferably 2,2,6,6-tetramethylheptane-3,5-dionate or acetylacetonate.

It will be understood by those skilled in the art that many of the compounds that are catalysts do not exist in simple monomeric form, but can be more highly coordinated or exist as "cluster compounds" or as "nonstoichiometric compounds". A review of yttrium and rare earth chemistry applicable to catalysts

of the present invention is R. C. Mehrotra, P. N. Kapoor, and J. M. Batwara, Chemical Reviews, Vol. 31, (1980),
pp 67-91. For a specific reference to the structure of yttrium alkoxides, see O. Pomlet et al., Inorg. Chem., 1989, 28, 263-267. O. Pomlet et al., J. Chem. Soc., Chem. Commun., 1989, 1846-1848. It is understood that even if such compounds do not exist as simple MZ_3 species, such compounds where the yttrium or rare earth metal is trivalent are included within the meaning of active catalysts, and are included within the meaning of structure MZ_3 in this specification. An example of such a cluster compound is $Y_3[OC(CH_3)_2]_7Cl_2(THF)_2$ in W. J. Evans and M. S. Sollberger, Inorganic Coordination Chemistry, Vol. 27(1988), pp 4417-4423.

The formula MZ_3 is also meant to encompass "complex" salts of yttrium and rare earth metals of the formula Me_2MZ_7, where M and Z have the meaning given above and Me is a divalent metal cation such as barium. Thus, the necessary elements in such compounds are trivalent yttrium or rare earth metal and one or more Z groups bound to them. Examples of such compounds are $Ba_2Y[OCH_2CH_2N(CH_3)_2]_7$ and $Ba_2Y(OCH_2CH_2OCH_2CH_3)_7$.

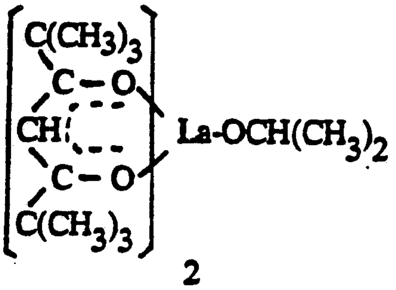
It will also be understood by those skilled in the art that if more than one type of Z group is present in a catalyst or mixture of two catalysts containing different Z groups is used, "redistribution" reactions may take place. By redistribution reactions is meant exchange of Z groups between metal atoms, so that it is possible, in theory, to obtain any combination of Z groups present on any particular metal atom.

By hydrocarbyl is meant any monovalent radical that contains only carbon and hydrogen. By substituted hydrocarbyl is meant any monovalent hydrocarbyl radical that contains other functional groups that do not substantially interfere with the reaction or react with any of the reactants or products. Suitable functional groups include halo, ester, ether, amino, thioether, silyl, hydroxy, carbon-carbon unsaturation (i.e., double or triple bonds) and aldehyde. Trivalent yttrium and rare earth compounds will not be stable if they contain a functional group whose pKa is less than that of the pKa of the conjugate acid of the functional group bonded to the yttrium or rare earth metal. A special case may arise when the two pKas are approximately equal. Then an equilibrium may exist as to which group is bound to the yttrium or rare earth metal, and if such groups fit the definition of Z above then both will initiate polymerization.

The polymerization of the present invention is carried out in the absence of any solvent in the molten lactide at from 100 to 220 °C, preferably from 110 to 200 °C and most preferably from 165 to 180 °C

It is preferred to use a dry inert gas such as nitrogen or argon to blanket the reaction. Moisture is deleterious to the stability of the catalyst and can limit the molecular weight of the polymer produced. The starting materials should be dry. Drying methods are known to those skilled in the art, and include distillation from calcium hydride passage over molecular sieves or crystallization.

The preferred catalyst is lanthanum bis(2,2,6,6-tetramethylheptane-3,5-dionato)isopropoxide



The catalyst must be stable at the reaction temperature which eliminates many of the known yttrium and rare earth metal compounds otherwise available.

The advantages of the process of the present invention are that it is faster, provides a narrow molecular weight distribution, provides a product with a better thermal stability as determined by weight loss at 200 °C and involves fewer side reactions as observed by color formation than many of the highly active catalysts in the literature.

Example 1

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 165 °C vapor bath. 35 microliters of a 0.25M solution of lanthanum bis(2,2,6,6-tetramethylheptane-3,5-dionato)isopropoxide in tetrahydrofuran was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 4000/1. The clear, colorless mixture becomes viscous immediately and shows no flow behavior after 1 minute. After an additional 1 minute, the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 92%. The molecular weight (gel permeation chromatography in tetrahydrofuran vs. polystyrene standard) was Mp=107,000, Mw=146,000, Mn=57,000, and Mw/Mn=2.6.

Example 2

Example 1 was repeated except the reaction temperature was 110 °C and the reaction time was 6 minutes. Monomer conversion was 98%. Mp=132,000.

Example 3

Lanthanum bis(2,2,6,6-tetramethylheptane dionato) isopropoxide catalyst

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 110°C vapor bath. 70 microliters of 0.25 M tetrahydrofuran solution was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 2000/1. The clear, colorless mixture exhibits no flow behavior after 3 minutes. After an additional 2 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 93%.

Example 4

Lanthanum bis(2,2,6,6-tetramethylheptane dionato) isopropoxide catalyst

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 165 °C vapor bath. 23.1 microliters of 0.25 M tetrahydrofuran solution was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 6000/1. The clear, colorless mixture increases rapidly in viscosity. After 2 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 83%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=124,000, Mn=53,000, and Mw/Mn=2.3.

Example 5

Lanthanum bis(2,2,6,6-tetramethylheptane dionato) isopropoxide catalyst

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 165 °C vapor bath. 17.5 microliters of 0.25 M tetrahydrofuran solution was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 8000/1. The clear, colorless mixture increases rapidly in viscosity. After 2 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 66%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=89,000, Mn=42,000, and Mw/Mn=2.1.

Example 6

Yttrium bis(2,2,6,6-tetramethylheptane dionato) isopropoxide catalyst

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 179 °C vapor bath. 87 microliters of 0.2 M solution of yttrium bis (2,2,6,6-tetramethylheptane dionato) isopropoxide in 2-methyl-tetrahydrofuran was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 2000/1. The clear, colorless mixture increases in viscosity, turning slightly yellow at about 2.5 minutes. After an additional minute the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 82%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=131,000, Mn=46,000, Mp=93,200 and Mw/Mn=2.8.

Example 7

Yttrium bis(2,2,6,6-tetramethylheptane dionato) isopropoxide catalyst

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 179 °C vapor bath. 43.3 microliters of 0.2 M solution of yttrium bis (2,2,6,6-tetramethylheptane dionato) isopropoxide in 2-methyl-tetrahydrofuran was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 4000/1. The clear, colorless mixture increases in viscosity, turning slightly yellow at about 2.5 minutes. After an additional 3.5 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 73%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=117,000, Mn=49,000, and Mw/Mn=2.4.

Example 8

Yttrium bis(2,2,6,6-tetramethylheptane dionato) isopropoxide catalyst

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 166 °C vapor bath. 87 microliters of 0.2 M solution of yttrium bis (2,2,6,6-tetramethylheptane dionato) isopropoxide in 2-methyl-tetrahydrofuran was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 2000/1. The clear, colorless mixture increases in viscosity, and after an additional 3.5 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 76%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=117,000, Mn=48,000, and

Mw/Mn=2.43.

Example 9

Di-iodo-Samarium-1-benzyl-n-octyloxide

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 166 °C vapor bath. 864 microliters of 0.04 M solution of Di-iodo-Samarium alkoxide prepared according to J. Org. Chem., 49(11), p. 2045 (1984) from SmI_2, n-octanal and benzylbromide, was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 1000/1. The clear, bright yellow mixture increases in viscosity, fading in color as the reaction proceeds. After 10 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 65%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=66,000, Mn=16,000, and Mw/Mn=4.1.

Example 10

Yttrium bis(2,2,6,6-tetramethylheptane dionato) dimethylaminoethoxide

5g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 166 °C vapor bath. 217 microliters of 0.08 M solution of yttrium bis(2,2,6,6-tetramethyl-heptane dionato) 2-dimethylaminoethoxide in toluene was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 2000/1. The clear, colorless mixture increases in viscosity, and after 10 minutes the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was 51%. Gel permeation chromatography in tetrahydrofuran vs. polystyrene standard gave Mw=96,000, Mn=48,000, and Mw/Mn=2.0.

Comparative Example 1

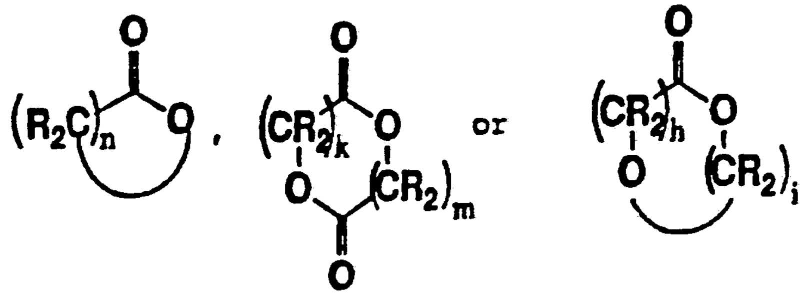
Polymerization using one of the catalysts preferred for solution polymerization

2g L-lactide, polymer grade, was melted in a flame-dried, nitrogen-flushed glass test tube suspended in a 165 °C vapor bath. 11 microliters of a 1.0 M solution of yttrium tris (N,N-dimethylaminoethoxide) in tetrahydrofuran was injected via hypodermic syringe to give a monomer to catalyst molar ratio of 1250/1. The clear, colorless mixture turns yellow upon mixing and shows very little viscosity increase through 10 minutes, when the tube was quenched in ice water to stop the reaction. Monomer conversion as measured by thermogravimetric analysis was only 43%. After precipitation of a methylene chloride solution of the reaction mixture into 10 volumes of methanol, gel permeation chromatography in tetrahydrofuran vs. polystyrene standard) gave Mw=33,000, Mn=24,000, and Mw/Mn=1.4.

Having thus described and exemplified the invention with a certain degree of particularity, it should be appreciated that the following claims are not to be so limited but are to be afforded a scope commensurate with the wording of each element of the claim and equivalents thereof.

CLAIMS

1. A process for polymerizing lactide comprising melting at 100 to 220 °C a lactide and up to 20 mole percent of another lactone of the formula



where n is 4 or 5, h, i, k and m are independently 1 or 2, each R is independently selected from H or hydrocarbyl containing up to 12 carbon atoms or substituted hydrocarbyl containing up to 12 carbon atoms with a catalyst of the formula MZ_3, wherein M is yttrium or a rare earth metal and at least one Z is $-OCR'_3$ where R′ is independently hydrogen, hydrocarbyl or substituted hydrocarbyl, the remaining two Zs can be fluoride, chloride, bromide, iodide, carboxylate, tetrasubstituted porphyrinato (-2), betadiketone anions, beta keto ester anions, cyclopentadienide, phenoxide or pentamethylcyclopentadienide, and cooling the resulting polymer.

2. The process of Claim 1 wherein the mole ratio of monomer to catalyst is from 500 to 20,000.

3. The process of Claim 2 wherein a lactide homopolymer is produced.

4. The process of Claim 1 wherein the R in the lactone co-monomer is H or CH_3.

5. The process of Claim 4 wherein the mole ratio of monomer to catalyst is from 500 to 20,000.

6. The process of Claim 1 wherein the lactone co-monomer is epsilon-caprolactone, delta-valerolactone, glycolide, 1,5-dioxepan-2-one or 1,4-dioxan-2-one.

7. The process of Claim 6 wherein the mole ratio of monomer to catalyst is from 500 to 20,000.

8. The process of Claim 1 wherein the polymerization is carried out at 110 to 200 °C.

9. The process of Claim 1 wherein two of the -Zs are 2,2,6,6,-tetramethylheptane dionato, or acetylacetonate.

10. The process of Claim 9 wherein the third -Z is isopropoxy, 2-ethoxyethoxy or 2-(N,N-dimethylamino)ethoxy.

11. The process of Claim 1 wherein M is lanthanum.

12. The process of Claim 9 wherein M is lanthanum.

13. The process of Claim 12 wherein the third Z is isopropoxy, 2-ethoxy ethoxy, or 2-N,N-dimethylethoxy.

14. The process of Claim 1 wherein the polymerization is carried out at 165 to 180 °C.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/11308

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 08 G 63/84 C 08 G 63/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 08 G

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	WO,A,9105001 (DU PONT DE NEMOURS AND CO.) 18 April 1991, see claims 1-15,29-30; page 5, line 17 - page 9, line 6; page 13, line 6 - page 14, line 22 (cited in the application) ---	1-14
P,A	WO,A,9204394 (DU PONT DE NEMOURS AND CO.) 19 March 1992, see claim 1; example; page 9, line 18 - page 12, line 26 ---	1
A	Macromolecules, vol. 21, no. 2, February 1988, (Washington, DC, US), H.R. KRICHELDORF et al.: "Poly(lactones). 9. Polymerization mechanism of metal alkoxide initiated polymerizations of lactide and various lactones", pages 286-293 -----	1

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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IV. CERTIFICATION

Date of the Actual Completion of the International Search 31-03-1993	Date of Mailing of this International Search Report 03. 05. 93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer D.H. KRISCHE

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9211308

SA 68687

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 13/04/93
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 9105001	18-04-91	US-A-	5028667	02-07-91
		AU-A-	6624490	28-04-91
		CA-A-	2066029	30-03-91
		CN-A-	1051367	15-05-91
		EP-A-	0493529	08-07-92
		US-A-	5095098	10-03-92
WO-A- 9204394	19-03-92	AU-A-	8440591	30-03-92
		CN-A-	1059734	25-03-92

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