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NOVEL DEGRADABLE ENGINEERING POLYESTERS—SYNTHESIS AND APPLICATIONS

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INTRODUCTION

Some groups of polymers exhibiting high strength and excellent mechanical properties during long-time service are considered to be high tech engineering materials. A great deal of research has been done on such materials; the outstanding achievements of Herman Mark and his students (e.g., Carl Marvel and Otto Vogl) should be mentioned. The work of these researchers stimulated progress in all branches of the modern technology, and contributed significantly to the present state of art in this field.

Nowadays, however, another group of polymer materials is also playing an important role. These are biodegradable polymers designed for service during a terminated period of time. The importance of these materials is due to their numerous applications in medicine and biology, as well as to their utility in the recycling of polymers.

The most common biodegradable polymers are aliphatic polyesters. Many types of biodegradable polyesters are produced in nature, e.g., by some microorganisms [1]. In synthetic chemistry, polycondensation, i.e., step-growth polyesterification, is the traditional method of polyester synthesis. Nowadays, however, great attention is being paid to lactones polymerization aimed at the synthesis of high molecular weight polyesters and such specialty polymers as biodegradable polyesters for medical applications, e.g., controlled drug-release systems. Past decades have brought about an enormous growth of research on the fundamental aspects of lactones and the polymerization of related monomers [2]. The chemistry of β-lactones polymerization is very important because of the utility of the polymers obtained as materials for medical applications. Besides the synthesis of biodegradable polymers by the polymerization of β-methyl-β-propiolactone (β-butyrolactone) [3–5], the base alcoholysis of an α,α-diphenyl-β-propiolactone has been studied with the expectation of preparing the corresponding analogues of tropic acid esters which exert antispasmodic activities [6].

In this paper some new aspects of the polymerization of lactones are discussed from both mechanistic and synthetic points of view.

β-LACTONES POLYMERIZATION WITH ALKALI METAL ALKOXIDES AS INITIATORS

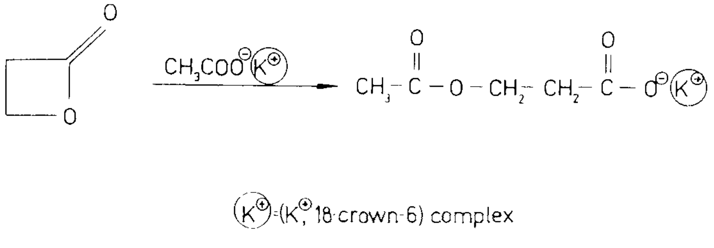
The mechanism of anionic polymerization of β-lactones initiated with weak bases such as alkali metal carboxylates or amines is well established: alkyl oxygen bonds of monomer molecules are cleaved and the carboxylate anions formed act as propagating species [7] (Scheme 1).

According to Lenz, the polymerization of α,α-disubstituted β-lactones proceeds without transfer and termination reactions, similar to the "living polymerization" of vinyl monomers first described by Ziegler [8] and Szwarc [9].

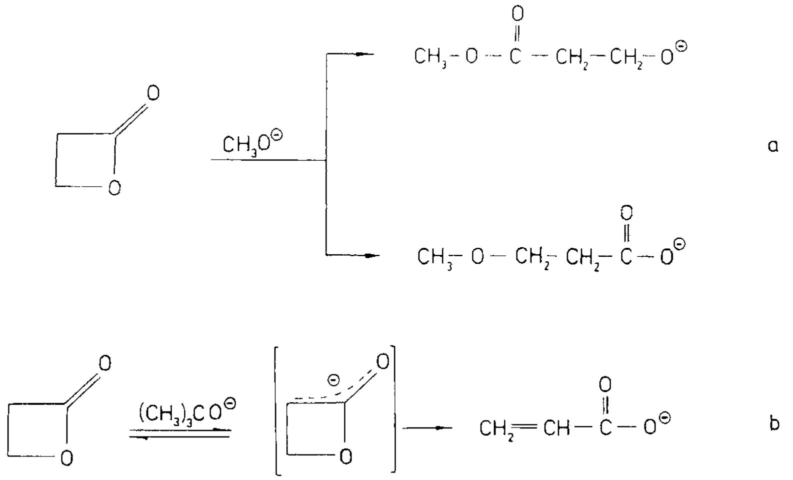
However, in β-propiolactone polymerization initiated by strong bases, such as potassium methoxide, the scission of both heterobonds of a monomer (acyl-oxygen or alkyl-oxygen) and incorporation of the initiator as an end group into a growing polymer chain was claimed, and that resulted in the formation of potassium salts of β-methoxypropionic acid and β-hydroxypropionic acid methyl ester as the initial products of polymerization [10] (Scheme 2a). These results suggested that potassium *tert*-butoxide in THF solution deprotonates β-propiolactone or butyrolactone, and the lactone enolates initially formed propagate polymer growth, yielding polymers with unsaturated double bonds as end groups [11, 12] (Scheme 2b).

On the other hand, it was found by Bartlett and Rylander [13] that the model reaction between β-propiolactone and potassium methoxide proceeds via several steps: (1) First, methanolysis and ring cleavage of the β-lactone takes place due to acyl-oxygen bond scission. (2) In the second step, base-catalyzed dehydration yields methyl acrylate, which after the next addition of methanol to the double bond (3) yields methyl β-methoxypropionate. The eventual hydrolysis of the latter by the water produced in the previous (2) step may yield β-methoxypropionic acid (Scheme 3).

The discrepancies existing in the literature necessitated further reinvestigations

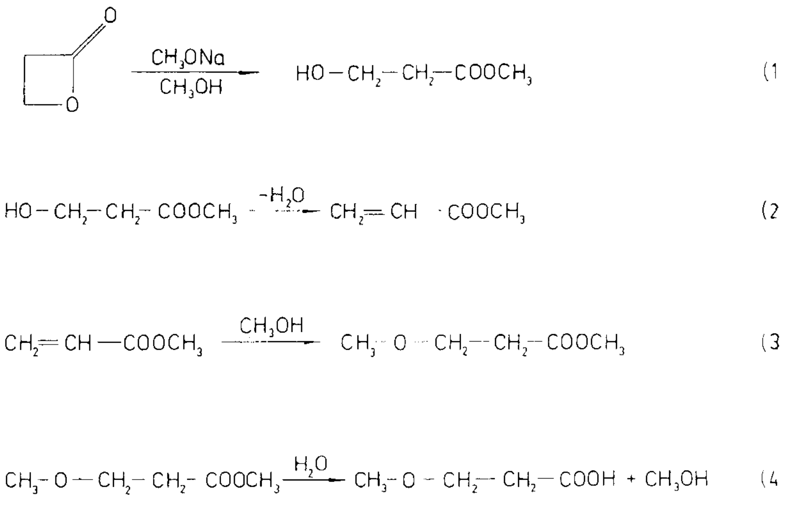


SCHEME 1.

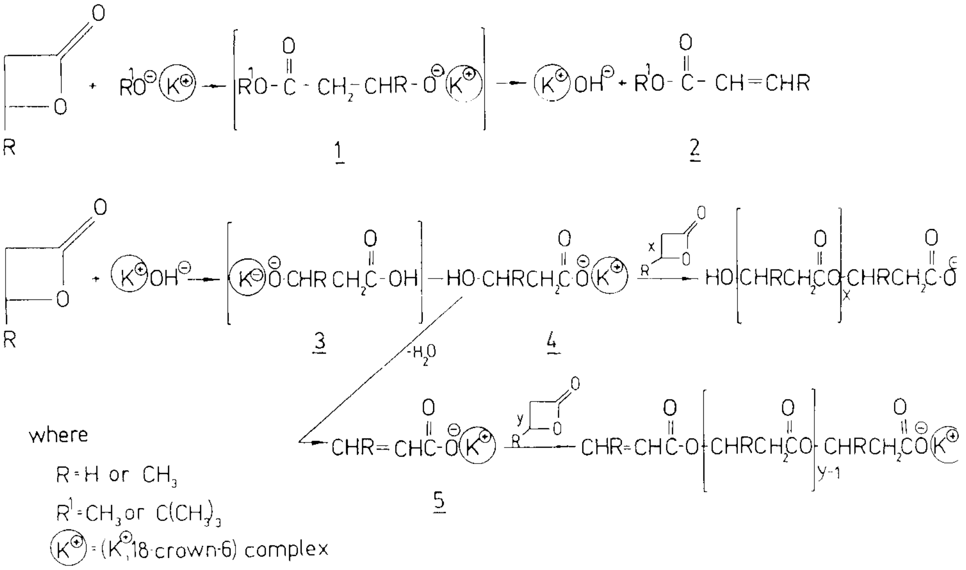


SCHEME 2.

of the common polymerization of β-lactones initiated by alkali metal alkoxides. The ^{1}H-NMR measurements indicate that an alkoxide initiator is not incorporated into the polymer chain, thus two types of end groups are present in the polymers obtained: unsaturated C=C bonds and hydroxy groups [14]. The equimolar model reactions of potassium methoxide or *tert*-butoxide with β-propiolactone or β-butyrolactone yield the corresponding unsaturated ester and potassium hydroxide, the latter acting as the real initiator. According to these results, the mechanism of β-lactones (unsubstituted or bearing methyl in the β-position) shown in Scheme 4 may be proposed.



SCHEME 3.

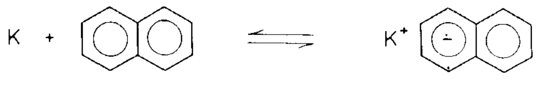


SCHEME 4.

The initiator-alkoxide anion attacks the carbonyl atom of β-lactone, inducing acyl-oxygen bond cleavage. The initial product—potassium β-alkoxide ester **1**—after the elimination reaction, yields the corresponding unsaturated ester **2** (unreactive in further polymerization) and potassium hydroxide. The latter reacts with the next molecule of β-lactone, inducing acyl-oxygen bond scission and producing unstable intermediate **3**. After rearrangement, this intermediate yields the corresponding potassium salts of β-hydroxy and unsaturated acids **4** and **5**, inducing further chain growth. Eventually polyesters with hydroxyl or unsaturated dead end groups are formed due to the propagation on carboxylate active centers. These results provide new evidence for β-lactones polymerization by alkali metal alkoxides and bring to an end the long-time controversy [15].

POLYMERIZATION OF LACTONES INITIATED WITH ALKALI METAL NAPHTHALENIDES

Alkali metals such as sodium or potassium react with naphthalene (or other aromatic compounds) with the formation of the corresponding naphthalenides due to electron transfer from the outer orbital of a metal to the aromatic acceptor (Scheme 5).



SCHEME 5.

Naphthalenides have been previously employed as efficient initiators of styrene polymerization [9, 16]. The initiation proceeds via electron transfer from a naphthalenide toward a styrene molecule, involving formation of the styrene radical anion [17]. Ring-opening polymerization of oxiranes [18], thiiranes [19], and thiethane [20] has been also accomplished using this initiator. However, sodium naphthalenide has been claimed not to polymerize β-lactones at room temperature [21]. After the addition of a crown ether (18C6) or a cryptand (C222), which is able to complex sodium or potassium anions, the equilibrium depicted in Scheme 5 is obviously shifted to the right, and this modified initiator is able to polymerize β-propiolactones, yielding "living polymers" with narrow molecular weight distributions. The ^{1}H-NMR spectrum of the polymer obtained, Fig. 1, indicates the presence of unsaturated double bonds and the absence of any naphthalene moieties from the initiator (Fig. 1). However, hydrogenated naphthalene was found in the reaction mixture.

According to these experimental results, the polymerization mechanism of Scheme 6 may be proposed. At the initiation step, a lactone enolate is formed due to α-proton abstraction from the β-lactone molecule, and hydronaphthalene is formed as a side product. Rearrangement of the lactone enolate leads to potassium crotonate (or acrylate). The latter, in the presence of a metal complexing agent (cryptand or crown ether), is capable of acting as an initiator. The polymerization proceeds via alkyl-oxygen bond scission, with carboxylate anions as the propagating species. Other evidence for the proposed mechanism was provided by the outcome of a model reaction (monomer:naphthalenide molar ratio = 1:1). The observation that polymerization of β-butyrolactone and β-propiolactone initiated with potassium naphthalenide proceeds only after the addition of a complexing agent, e.g., 18-crown-6, indicates that the propagation is operating because of loose ion pairs

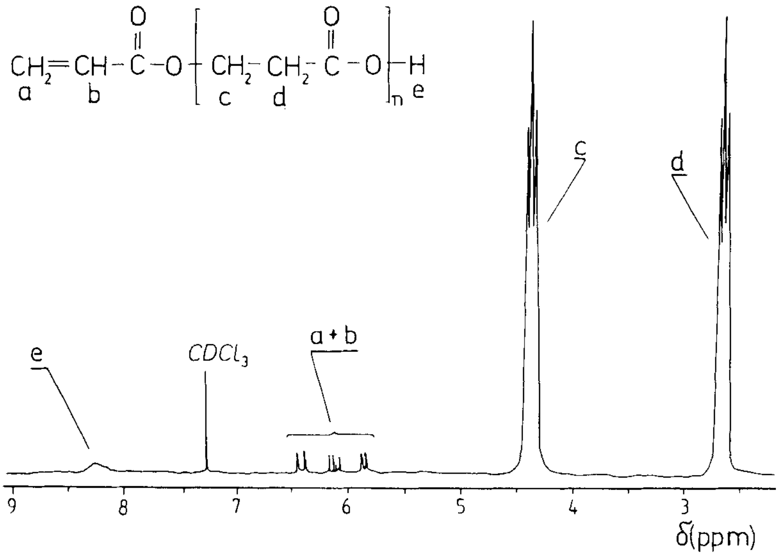
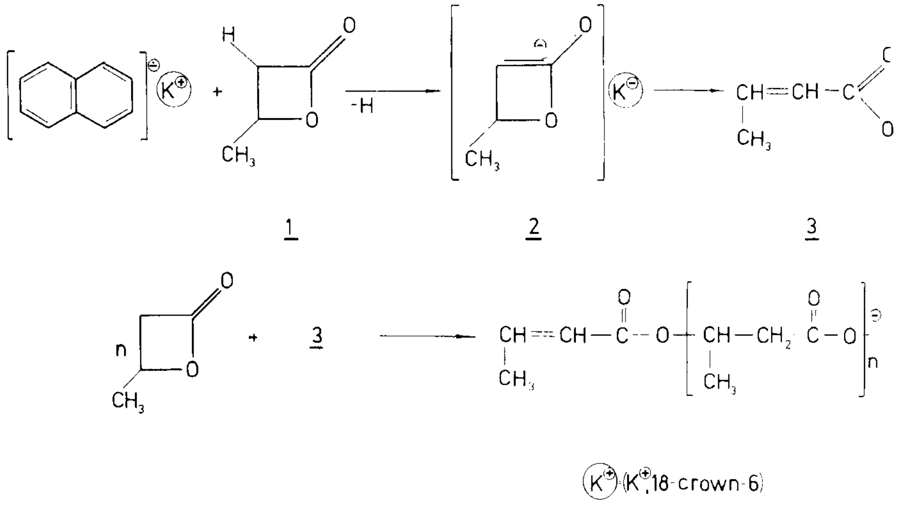


FIG. 1. ^{1}H-NMR spectrum of poly(β-propiolactone) obtained with potassium naphtalenide/18C6 complex as initiator.



SCHEME 6.

TABLE 1. Results of Anionic Polymerization of β-Lactones Initiated by Potassium Naphthalenide (at 20°C)

Monomer	Cation complexing agent	$[M]_0/[I]_0$	Time, h	Yield, %	M_n	M_w/M_n[b]
β-Propiolactone	None	50[c]	20	10	–	–
β-Propiolactone	18-Crown-6	40[c]	5	92	2,500	–
β-Propiolactone	Cryptand [2,2,2]	200[d]	10	90	13,600	–
β-Propiolactone	Cryptand [2,2,2]	2000[d]	24	89	120,500[e]	–
β-Butyrolactone	None	50[c]	200	8	–	–
β-Butyrolactone	18-Crown-6	40[c]	96	90	2,800	1.28
β-Butyrolactone	Cryptand [2,2,2]	40[c]	96	98	2,950	1.22
β-Butyrolactone	Cryptand [2,2,2]	75[d]	110	97	6,200	1.25
β-Butyrolactone	Cryptand [2,2,2]	150[d]	200	95	11,000	1.29

[a] Number-average molecular masses were determined by the VPO technique in $CHCl_3$ using a Knauer vapor pressure osmometer.

[b] Determined by GPC according to polystyrene standards with a low polydispersity.

[c] Conducted in THF, M_0 = 2.0 mol/L.

[d] Conducted in THF, M_0 = 3.0 mol/L.

[e] Estimated from viscometric measurement.

or free anions, producing telechelic polymers with narrow molecular weight distributions (Table 1).

It is interesting to notice that the mechanism of β-lactone ring-opening reactions with alkali metal naphthalenides differs from that operating in styrene polymerization. In the polymerization of styrene, the transfer of an electron occurs from the initiator to the styrene monomer. In the polymerization of β-lactone, however, the proton transfers from the monomer to the naphthalene radical anion, resulting in naphthalene protonation. Polymerization of γ-lactones with sodium or potassium naphthalenide does not take place because of the thermodynamic stability of 5-membered lactones [22]. However 6-membered δ-valerolactone polymerizes easily, yielding living polyesters, with α-proton abstraction from the monomer being the first step of the initiation process [23].

POLYMERIZATION OF LACTONES WITH ALKALI METAL SUPRAMOLECULAR COMPLEX AS ELECTRON TRANSFER CATALYST

The discovery by Pedersen [24] and Lehn [25] of crown ethers, cryptands, and other organic ligands capable of complex metal cations has opened new perspectives in chemical research. In the early 1970s it was revealed that such alkali metals as sodium, potassium, rubidium, and cesium can be easily dissolved in etheral solvents, e.g., tetrahydrofuran, after addition of a macrocyclic ligand. The metal "blue" solutions contain complexed metal cations associated with metal anions and solvated electrons [26]. These alkali metal organic solutions have been employed as organic reagents [27, 28] and initiators for the polymerization of butadiene, vinyl monomers, and some sulfur-containing monomers [29–32]. Based on kinetic studies on metal solubilization we were able to rationalize the process of metal dissolution, thus showing that under proper conditions (time, temperature), metal solutions containing metal ions but only a small, negligible amount of electrons could be produced [33]. Novel initiators with a well-defined concentration of metal ions, controlled by metal NMR measurements [34, 35], were prepared in a simple manner by dissolution of a solid metal, e.g., potassium mirror or sodium–potassium alloy (1:1), in an organic solvent, like THF or tetraglyme, containing an organic ligand. The latter attracts cations, forming supramolecular metal complexes with the following formulas:

$K^+/15C5/,K^-$

$K^+/18C6/,K^-$

$K^+/\text{glyme}/,K^-$

$K^+/15C5/,Na^-$

where 18C6 = 18-crown-6, 15C5 = 15-crown-5.

It turned out that in the polymerization of substituted and unsubstituted β-lactones, as well as lactides, the initiation is very fast and "living" polymers are produced, as evidenced by GPC and kinetic measurements [36] (Fig. 2).

Due to the "living character" of this polymerization, the use of novel initiators enables the preparation of block polymers, e.g., diester blocks of β-propiolactone

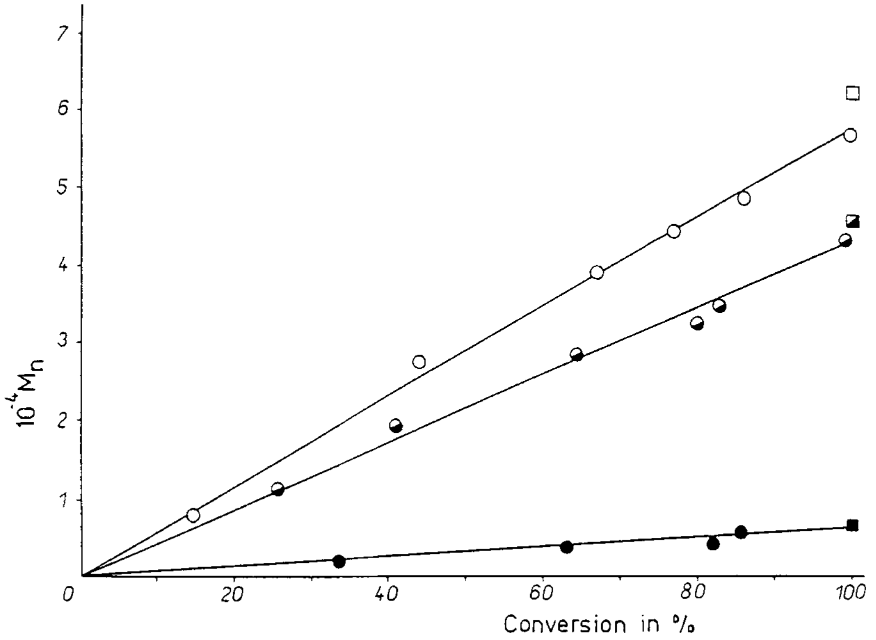


FIG. 2. Dependence of M_n/conversion for poly(β-lactones) obtained in the presence of potassium solution: (◑) β-propiolactone, (◪) M_n(calc) = 46,000; (○) α,α-methylethyl-β-propiolactone (□), M_n(calc) = 62,900; (●) β-butyrolactone, (■) M_n(calc) = 6700.

and β-butyrolactone, styrene–lactone [37] and acrylate–lactone blocks. These block polymers are degradable in suitable environmental conditions or they can be hydrolyzed, which is important in recycling processes. On the other hand, polymers of β-methyl-β-propiolactone (β-butyrolactone) can serve as models of natural poly-β-hydroxybutyrates produced by some bacteria as storage material in their cells [1]. These polymers are biodegradable and bioresorbable, and they may be used for medical applications such as controlled drug release.

The question arises: What is the mechanism of this unusual polymerization? End-group analysis revealed that acetoxy end groups are present in the polymers (or oligomers) formed, and the carboxylate anions are propagating species, as indicated by ^{1}H-NMR spectroscopy (Fig. 3).

The results of model reactions carried out in the NMR instrument tube and followed by ^{39}K-NMR spectroscopy suggest that two electrons are transferred from the metal anion to a monomer molecule at the initiation step of polymerization, as evidenced by the signal of the potassium anion vanishing completely after addition of the monomer, the signal of the potassium cation being broadened (Fig. 4).

Model reactions between β-lactone monomer and potassium anion (molar ratio 1:1) revealed that uncommon α-carbon to β-carbon bond scission takes place and that enolate carbanion is formed as an initial product of the ring cleavage of a monomer, as evidenced by analysis of the final products of this reaction after protonation or methylation (Scheme 7).

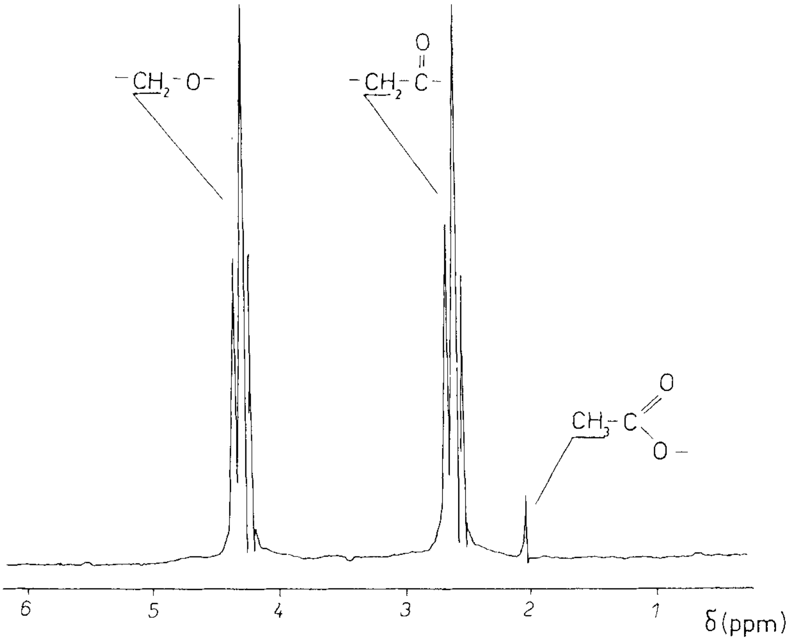


FIG. 3. ^{1}H-NMR spectrum of poly(β-propiolactone) obtained with potassium solution as initiator.

The mechanism of this reaction is a general one, valid for substituted and unsubstituted β-lactone monomers [38]. As proven by ESR measurements, the reaction first involves single electron transfer from metal anion to β-lactone molecule, resulting in the formation of a lactone radical anion (Scheme 8). The latter, being unstable, undergoes β-elimination to form an enolate radical, as observed in the ESR spectra (Scheme 8). This radical reacts with potassium to form the corresponding enolate carbanion which exists in mezomeric forms stabilized by resonance [39]. It may be assumed that the driving force of this reaction is the stabilization effect, guiding the reaction along the thermodynamically most convenient route. When a monomer is available in excess in common polymerization conditions, the enolate carbanion initially formed attacks the monomer to produce growing polymer chains. The propagation proceeds via alkoxide (Scheme 8) and carboxylate active centers, formed due to acyl-oxygen and alkyl-oxygen bond scission of a monomer. Alkyl-oxygen bond cleavage prevails at higher conversion, and polymers having carboxylate active centers are eventually produced [36] (Scheme 9).

The proposed mechanism is very complex, involving scission of α-carbon to β-carbon bonds of a β-lactone monomer (at the initiation step) and cleavage of both heterobonds, i.e., acyl-oxygen and alkyl-oxygen, at the propagation step. In spite of the complexity of this polymerization, the properties of the final polymers can be strictly controlled due to the living character of this process.

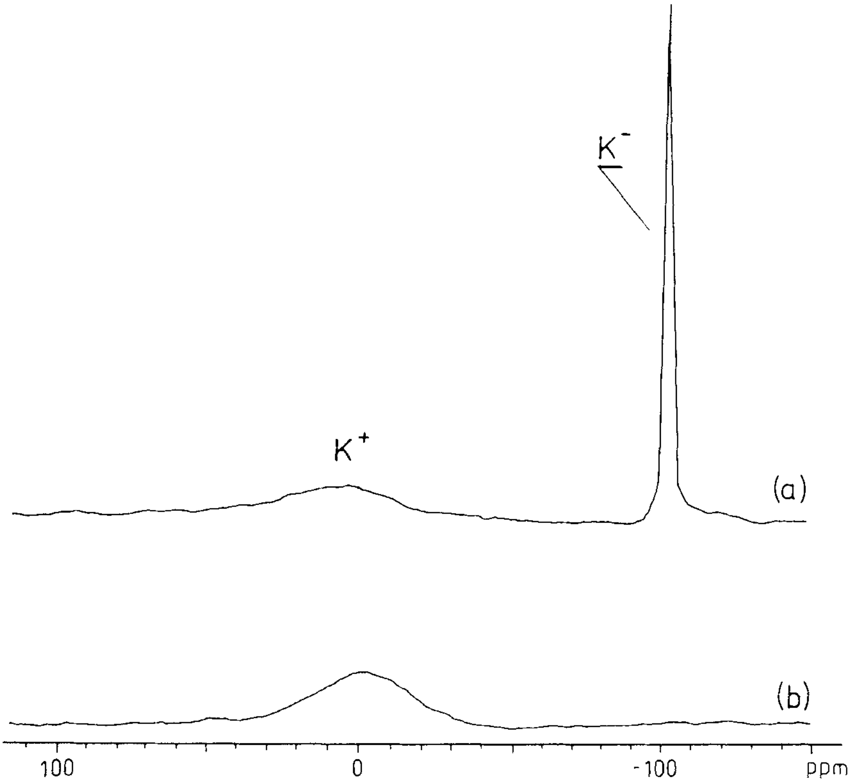
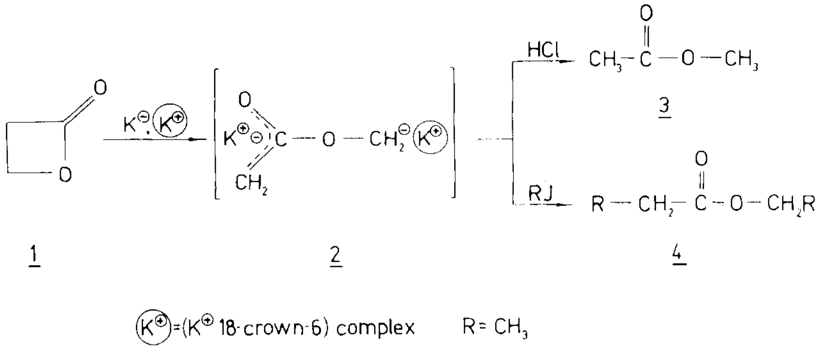


FIG. 4. ^{39}K-NMR spectra of (a) the potassium solution obtained by complexation of K with 18C6 in THF, and (b) the mixture after treatment with β-propiolactone.



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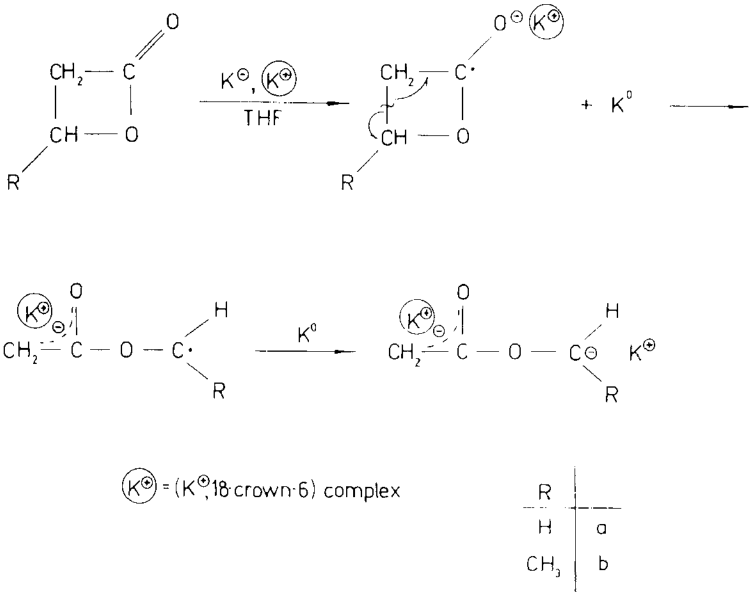
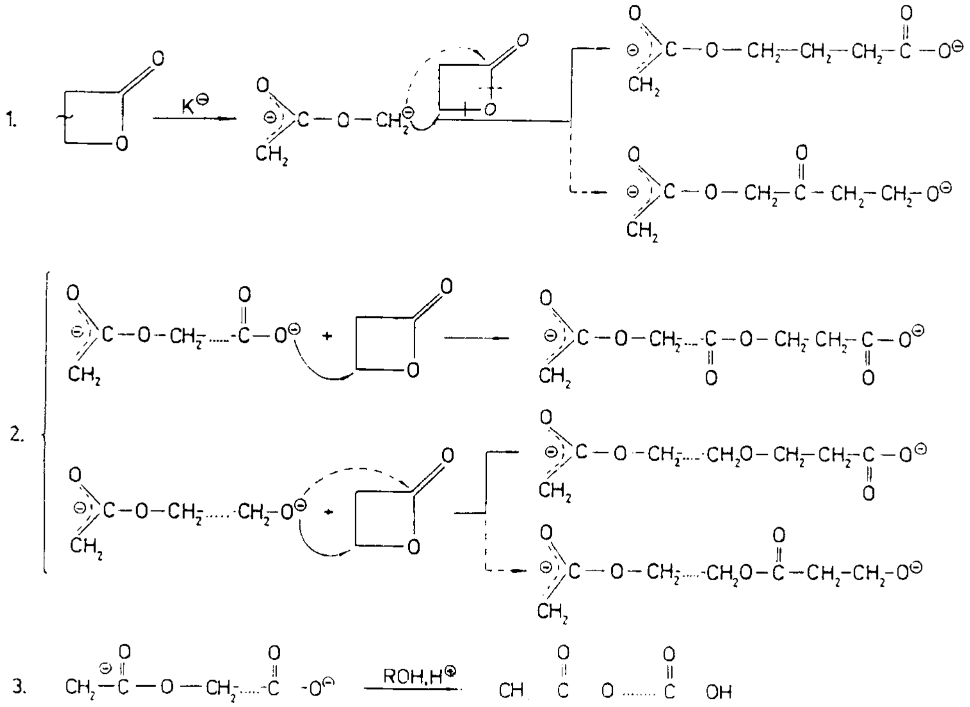


SCHEME 8.



SCHEME 9.

CONCLUSIONS

The ring-opening polymerization of simple lactones constitutes a convenient method of synthesizing aliphatic polyesters. Some of polyesters produced by ring-opening polymerization exhibit such unique properties as biodegradability, bioresorbability, and nonimmunogenity, and therefore are considered to be very interesting materials for medical applications. On the other hand, vinyl-ester block polymers offer novel applications as materials for the packing industry because they can conveniently be recycled. Novel catalysts and initiators and the novel chemistry of the polymerization of lactones have been reviewed in this paper.

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