Acta Chemica Scandinavica, 1999: 53: 157–162
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Review Article

Ring-Opening Reactions of β-Lactones with Activated Anions

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Jedliński, Z., 1999. Ring-Opening Reactions of β-Lactones with Activated Anions. – Acta Chem. Scand. 53: 157–162. © Acta Chemica Scandinavica 1999.

The mechanistic aspects of β-butyrolactone ring-opening reactions with various activated anions, their regioselectivity and stereochemistry are discussed. The facile synthesis of biomimetic polyesters having similar microstructure and properties as produced in Nature, such as poly-(*R*)-3-hydroxybutanoic acid, has been accomplished.

Anion-promoted reactions are very common in organic chemistry, e.g. in aliphatic and aromatic nucleophilic substitution, alkylation, oxidation, as well as in addition and elimination reactions. These reactions are usually performed in homogeneous solutions or in heterogeneous phase transfer catalysis (PTC) systems.[1–5]

Anion reactivity depends very strongly on interactions with the surrounding molecules. Cation–anion association and solvent–anion interactions are important factors determining anion reactivity. The influence of various solvents on anion reactivity has been studied in many nucleophilic substitution reactions.[6]

In homogeneous solutions of anionic species there exist the following equilibria, where L denotes ligand capable of cation complexation.

$$\underset{\text{ion pairs aggregates}}{(M^+A^-)_n} \rightleftharpoons \underset{\text{contact ion pairs}}{M^+A^-} \rightleftharpoons \underset{\text{solvent separated ion pairs}}{M^+(\text{solv.})\ A^-} \overset{L}{\rightleftharpoons} \underset{\text{loose ion pairs}}{M^+L,\ A^-}$$

The equilibria in such systems are shifted to the right after addition of a cyclic or an open-chain ligand (crown, cryptand, glyme, etc.) capable of complexation of cations. The loose anion pairs, formed after cation complexation, usually become more reactive for two reasons: (1) complex formation of a cation leads to an increase in the rate of a given anionic reaction because an anion is activated due to its reduced interaction with bulky complexed cation, and (2) increased anion concentration due to the better solubilization of the reagent.

The concept of anion activation has been utilized in many organic reactions promoted by complexation of cations with crown ethers, cryptands, glymes or other complexing agents. A comprehensive review on anion activation has recently been published.[6] However, information is scarce on the ring-opening reactions of β-lactones with activated anions.

Some examples of lactone reactions with activated anions are provided in the following sections.

Reactions of β-lactones with activated alkali-metal alkoxides and carboxylates. New routes to biomimetic polyesters. Synthesis of tropic acid esters, via alcoholysis of α,α′-diphenyl-β-propiolactone, exhibiting antispasmodic activity,[7] as well as synthesis of biomimetic polyesters from β-lactones[8] have been reported.

Poly-β-lactones, particularly poly-β-butyrolactone, are produced by enzymes in Nature and they play an important role in life processes. A natural biopolymer containing (*R*)-3-hydroxybutanoic acid units (PHB) has been found in the cells of a great variety of microorganisms as intracellular carbon and energy storage material.[9] The low molecular weight PHB forms, together with calcium polyphosphonate, building blocks in membranes of prokaryotic and eukaryotic cells. It is also present in human blood plasma, thus it obviously plays an important role in life processes.[10,11] Therefore significant attention has been paid to the studies on the subtle structure of the native PHB and its analogues. The natural PHB isolated from bacterial cells consists entirely of *R* enantiomeric units and exhibits a high degree of crystallinity in spite of the fact that it is completely amorphous in native granules of PHB, (e.g. those present in *Bacillus megaterium*). PHB granules in native bacterial cells contain 97.7% PHB together with 1.9% proteins and 0.4% lipids, the latter presumably forming coatings around the pure PHB core.[12] It is assumed that such coatings slow down polymer crystallization because the tendency to nucle-

ation within granules is small and crystallization is retarded. In the course of the isolation of granules from bacterial cells by extraction with an organic solvents, instant polymer crystallization has been observed, due to the removal of coatings from granules.

A synthetic biomimetic polymer would be useful as a model of a natural one, e.g. for preparation of synthetic PHB granules, and also as membrane channels mimicking natural ones. A better understanding of the role of PHB in life processes and in potential medical applications is needed and therefore a great deal of research has been done on the synthesis of PHB analogues having polymer chain structure and end-groups similar to those in natural polymers (hydroxy and carboxylate end groups).

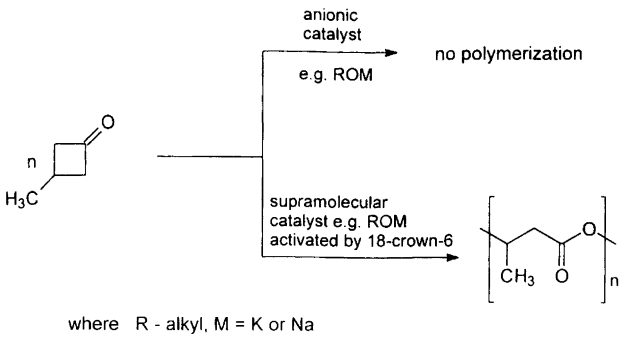
Many syntheses of PHB analogues via polycondensation with various titanium- and tin-based catalysts have been performed. However, polymers having rather low molecular weight were produced.[13] Seebach and his group[14] developed an elegant multistep condensation strategy starting from monomeric (*R*)-3-hydroxybutanoic acid using protection and deprotection of active groups at each condensation step. This method yielded well defined linear low molecular weight polymers and cyclic (*R*)-3-hydroxybutanoic acid oligomers, but was very laborious and time-consuming.

As an alternative to the polycondensation procedure, PHB oligomers and polymers have been synthesized via ring-opening polymerization of β-butyrolactone initiated by various coordinative catalysts.[15,16] However, the polymers obtained exhibited polymodal molecular weight distribution and the structure of polymer chains containing fragments of a metallic catalyst was different from that present in the natural poly-(*R*)-hydroxybutanoic acid.

Trying to synthesize poly-(*R*)-hydroxybutanoic acid similar to natural PHB present in living systems, we employed anionic initiators in the polymerization of β-butyrolactone. In an attempt to synthesize biomimetic poly-3-hydroxybutanoic acid, we employed (*S*)-β-butyrolactone as the monomer and potassium methoxide and *tert*-butoxide as catalysts. All these attempts failed. Unsubstituted β-lactone polymerized but β-butyrolactone turned out to be an unreactive monomer with anionic initiators.

The yield of the ring-opening reaction of β-butyrolactone could be enhanced only if a crown ether, e.g. 18-crown-6, was added to the potassium alkoxide and the activation of alkoxide anion occurred due to complexation of potassium cation (Scheme 1).

It turned out that polymerization proceeds regioselectively with inversion of configuration because a substitution–elimination mechanism is operative in this reaction.[17] Thus polymers with *R* configuration of the polymer chains could be synthesized if the *S*-monomer is used as the substrate. However, due to the substitution–elimination mechanism (Scheme 2), the polymer chains also contain a certain number of unsaturated crotonate end groups as confirmed by ESI-MS analysis (Fig. 1).



Scheme 1.

Thus the structure of synthetic polymers is similar but not identical with the native natural PHB polyesters.[18]

It has also been found that unsaturated end groups are formed in the polymerization of β-butyrolactone with activated potassium hydride (Scheme 3).

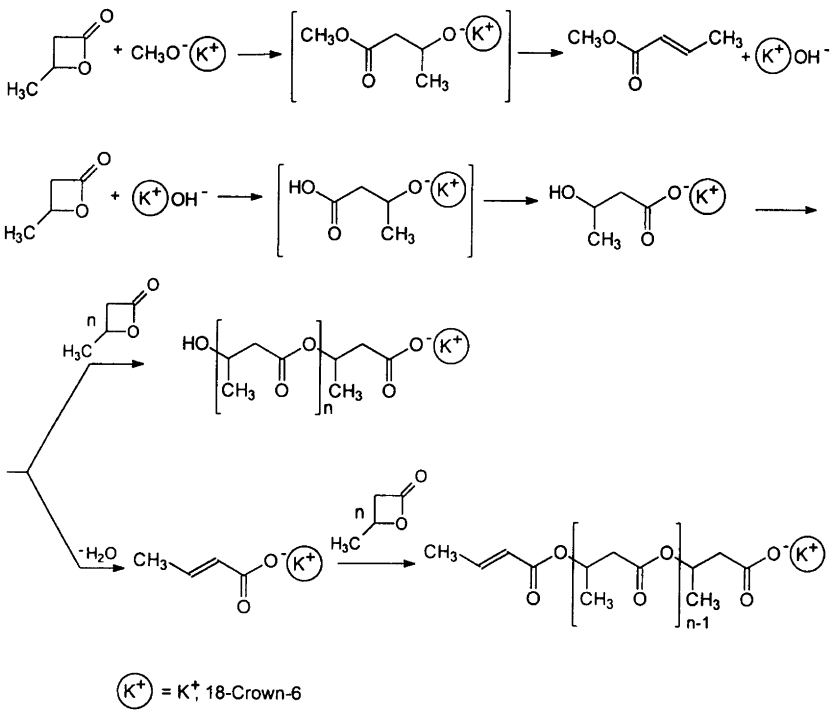
The fact that even small structural defects, such as unsaturated crotonate groups, can change the biochemical behaviour of a biopolymer meant that another regioselective initiator was needed able to produce poly-(*R*)-3-hydroxybutanoic acid bearing only –OH and –COOH end groups typical of natural PHB. Therefore, the ability of the sodium salt of (*R*)-3-hydroxybutanoic acid activated by a crown ether to function as an initiator was examined. The experimental results[19] showed that the polymerization of (*S*)-β-butyrolactone with this initiator, performed in bulk phase or in an organic solvent, proceeds regioselectively with inversion of configuration, yielding poly-(*R*)-3-hydroxybutanoic acid exhibiting the same stereochemistry and end groups as present in natural PHB (Scheme 4).

The hydroxybutanoic anion of the initiator attacks the chiral carbon atom of the monomer, as is usual in ring-opening reactions of β-lactones induced by carboxylate anion, implying alkyl–oxygen bond scission with the inversion of configuration at the chiral carbon atom (Scheme 4). The polymer chain growth proceeds entirely via carboxylate anions, and polymers formed bear hydroxy and carboxy end groups. The very small proportion of crotonate end groups, evidenced by ESI-MS spectroscopy, is negligible.

Thus linear monodisperse, optically active poly-(*R*)-3-hydroxybutanoic acid is formed exhibiting molecular weights of up to 15.000 with the use of this supramolecular complex of hydroxybutanoic acid salt as initiator (Table 1).

The molecular weight of the resulting linear polymers depends on the monomer-to-initiator molar ratio (Table 1). The molecular weight distribution is relatively narrow ($M_w/M_n \approx 1.1$–1.2), which is indicative of the uniformity of the polymers obtained. As evidenced by ^{1}H NMR spectroscopy (Fig. 2) the synthetic biopolymers are entirely isotactic and crystalline.[19]

Reactions of β-lactones with activated alkali-metal anions. Remarkable progress in organic chemistry and novel



Scheme 2.

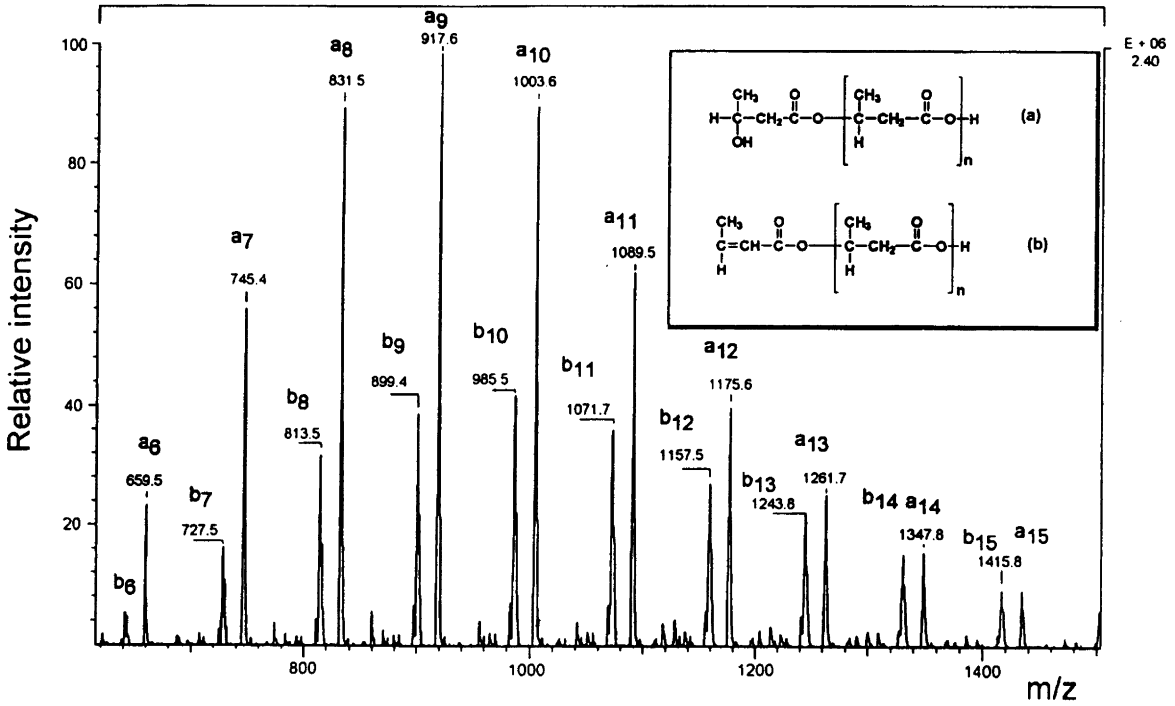
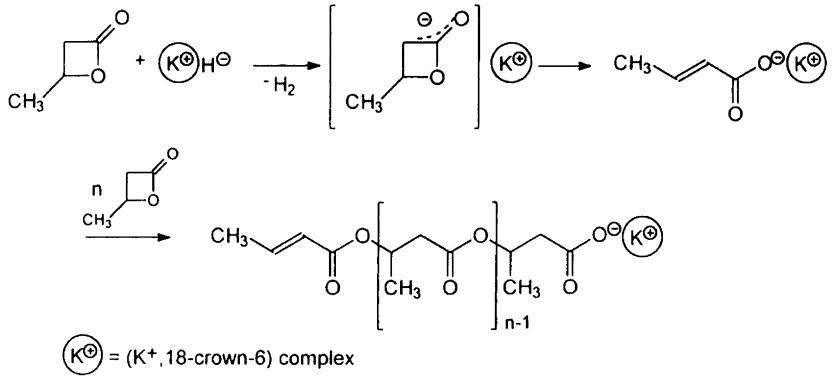
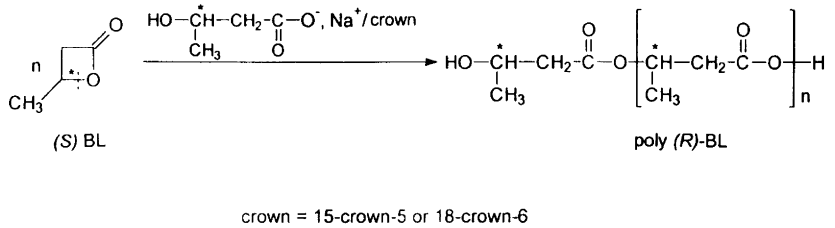


Fig. 1. ESI-MS spectrum of poly-(*R*)-3-hydroxybutanoic acid obtained with potassium methoxide–18-crown-6 as iniciator (M_n=1400). Two series of molecular ions, which differ by 18 Da (i.e., the molecular weight of water) assigned to polyester macromolecules with crotonate (b_n) and hydroxy (a_n) end groups respectively are visible. Indexes (*n*) of the peak labels (a_n, b_n) correspond to the number of hydroxybutyric units in butyrolactone oligomers.

possibilities are offered by supramolecular assistance to organic syntheses.[6] Macrocyclic ligands, crown ethers and cryptands capable of complexation of alkali-metal cations, are used to prepare alkali-metal solutions in low-polarity aprotic solvents such as tetrahydrofuran, dimethyl ether, and amines.[20] It has been demonstrated that controlled metal dissolution[21–23] yields unusual metal ion pairs in solution: M^+L, M^- (where L is a



Scheme 3.



crown = 15-crown-5 or 18-crown-6

Scheme 4.

Table 1. Results of anionic polymerization of (*S*)-β-butyrolactone[a] at room temperature initiated by various anionic initiators.[b]

Entry No.	Initiator[b]	Solvent	$[M]_0$ m/l	M_{ncalc}	Yield (%)	M_n	M_w/M_n	$\%iso_{calc}$[c]	%iso[d]	$[\alpha]_{365}^{25}$[e]
1	MeOK	THF	5.0	7.400	93	7.000	1.20	95	94	+9.8
2	MeOK	—	12.2	18.600	92	15.300	1.18	95	95	+9.3
3[f]	MeOK	—	12.2	40.000	96	37.100	1.08	50	50	—
4	HORCOONa[g]	THF	3.0	2.100	89	2.000	1.30	95	95	+7.0
5	HORCOONa[h]	THF	4.0	9.800	91	7.900	1.30	95	94	+6.5
6	HORCOONa[h]	—	12.2	10.800	94	8.100	1.30	95	95	+7.1
7	HORCOONa[h]	$CHCl_3$	4.0	11.800	96	10.500	1.01	95	95	+6.9
8[i]	HORCOONa[h]	THF	4.0	9.800	2	—	—	—	—	—
9[j]	*Alcaligenes eutrophus*	—	—	—	—	131.000	4.3	—	—	+7.4

[a](*S*)-β-Butyrolactone optical purity −95% ee. [b]Supramolecular complexes with crown ether. [c]Calculated isotactic diad fraction in percent. [d]Isotactic diad content determined by ^1H NMR spectroscopy from the intensities of methyl group signals. [e]$c = 0.028$ g cm^{-3} in $CHCl_3$. [f]Racemic monomer. [g]Racemic 3-hydroxybutanoic acid sodium salt. [h](*R*)-3-Hydroxybutanoic acid sodium salt. [i]Reaction without addition of crown ether. [j]Natural microbial polymer produced by *Alcaligenes eutrophus*, sample from Aldrich.

suitable complexant of the metal cation, e.g. crown ether, cryptand, or glyme, and M is potassium or sodium). It turns out that metal ion pairs are capable of transferring two electrons to suitable substrates to produce the respective carbanions[23,24] (Scheme 5). The versatility of this process enables facile preparation of various carbanions and offers novel opportunities in organic synthesis.[23]

The reaction of a β-lactone with potassium supramolecular complex proceeds smoothly yielding an enolate-carbanion as a result of unusual C–C scission in the strained β-lactone ring (Scheme 6). The driving force of this unique C–C bond cleavage in β-lactones is obviously the strong resonance stabilization of the intermediate enolate carbanion.[25,26] Such a course of reaction is valid for all β-lactones.

Synthesis of PHB, containing similar chain architecture as that in the natural product was accomplished by polymerization of (*S*)-β-butyrolactone with an alkali-metal supramolecular complex. However, in this case polyesters formed carry acetoxy end groups unknown in the natural product.

Conclusions

The results presented here show the great utility of activated anions in the ring-opening reactions of β-lactones. Even unreactive (*S*)-β-butyrolactone, bearing

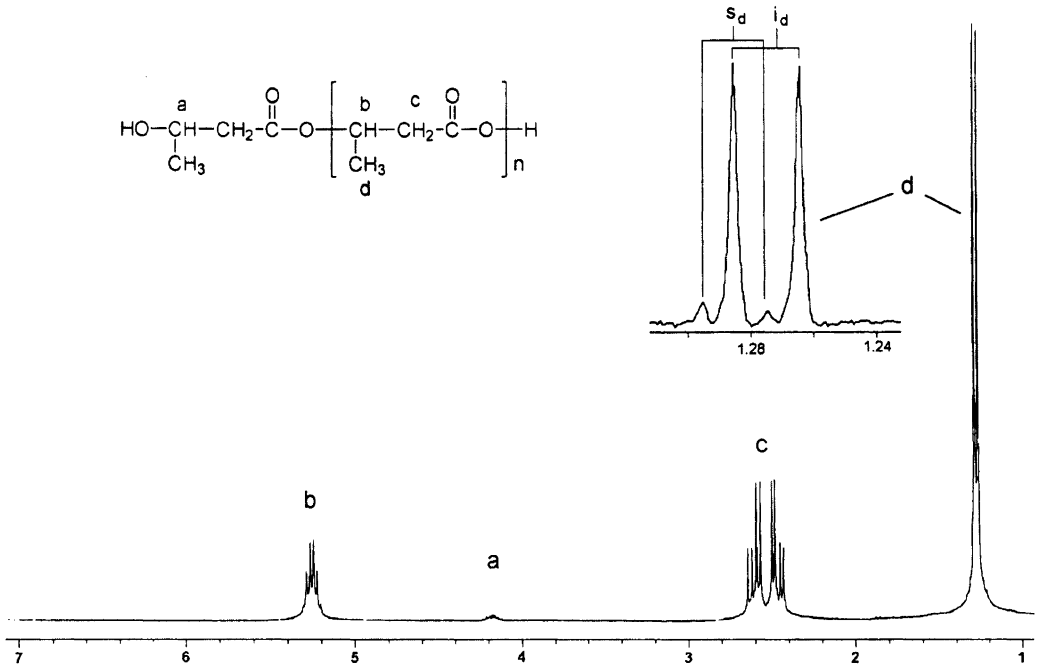
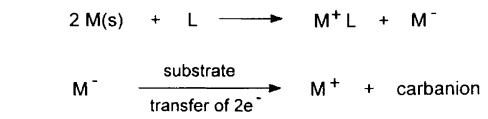
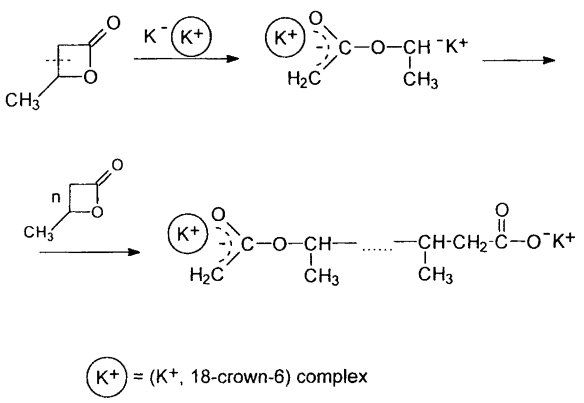


Fig. 2. ^{1}H NMR spectrum of poly-(*R*)-3-hydroxybutyric acid obtained with 3-hydroxybutanoic acid sodium salt–18-crown-ether as initiator; M_n=2000. In the expanded methyl group region the signals corresponding to *iso* (i_d) and *syndio* (s_d) diads are visible.



(where M is the alkali metal, e.g. potassium or sodium, and L is the complexant, e.g. 18-crown-6)

Scheme 5.



Scheme 6.

a methyl substituent on the β-carbon atom, polymerizes with activated alkali-metal alkoxides or carboxylates yielding biomimetic poly-(*R*)-3-hydroxybutanoic acid. Thus the synthesis of tailored polyesters similar to or identical with those synthesized in the cells of prokaryotic and eukaryotic organisms in Nature can be accomplished using supramolecular complexes as catalysts bearing activated carboxylate or alkoxide anions.

On the other hand, electron-transfer reagents, such as potassium or sodium supramolecular complexes consisting of alkali-metal ion pairs (i.e. the complexed metal cation and metal anion), are capable of causing C–C bond ring cleavage in the strained β-lactone ring and inducing polymerization.

The great versatility of the ring-opening reactions of β-lactones is worth emphasizing. Depending on the nature of a catalyst, its activation and the presence of alkyl substituents on the four-membered β-lactone ring, either alkyl–oxygen and acyl–oxygen or unique, carbon–carbon bond-scission can be observed. Supramolecular assistance to the ring-opening reaction of β-lactones is essential.

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Received August 21, 1998.