Nucleophilic Substitution and Electron Transfer in the Ring-Opening Reactions of β-Lactones: A Short Review

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***The paper dedicated in honor of Professor J. S. Bradshaw**

Nucleophilic substitution by activated organic anions and single- and two-electron transfer in ring-opening reactions of 4-membered β-lactones are described.

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Introduction.

The mechanism of organic reactions with nucleophilic reagents is very complex. These reactions are considered to proceed *via* nucleophilic substitution, but also electron transfer mechanisms have been proposed [1]. The distinction between outer-sphere or inner-sphere electron transfer reactions and classical substitution is difficult to make [2].

In this paper, recent results of anionic ring opening reactions of four member β-lactones are reported. Particular attention has been paid to the β-butyrolactone ring-opening reaction and polymerization of this compound yielding polymers which are analogous to natural poly(3-hydroxybutanoate), the so called PHB polymer, which is widely distributed in biological systems.

Scheme 1

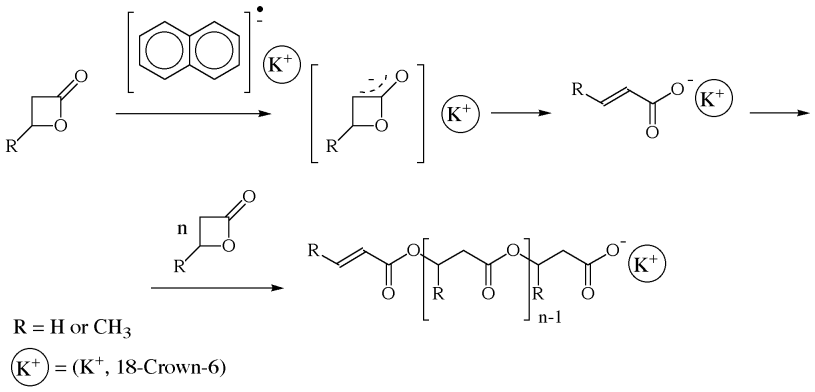


Table 1

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

Monomer	Cation-complexing agent	$[M]_o/[I]_o$	Time (hour)	Yield (%)	M_n(VPO)[a]	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[222]	200[d]	10	90	13,600	-
β-Propiolactone	cryptand[222]	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[222]	40[c]	96	98	2,950	1.22
β-Butyrolactone	cryptand[222]	75[d]	110	97	6,200	1.25
β-Butyrolactone	cryptand[222]	150[d]	200	97	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_o = 2.0 mol/L; [d] Conducted in THF, M_o = 3.0 mol/L; [e] Estimated from viscometric measurement.

The high molecular weight PHB is produced by a wide range of microorganisms as intracellular carbon and energy sources [3]. This polymer produced by enzymes is also present in the human body and plays an important role in life processes.

Ring-opening and anionic polymerization of this lactone constitute an alternative approach to PHB synthesis in contrast to enzymatic methods proceeding in nature. Knowing the mechanism for ring-opening of β-butyrolactone allowed the regio-selective synthesis of stereoregular [R]PHB, analogous to the natural PHB, to be demonstrated. The mechanisms of ring-opening of β-butyrolactone with following anionic catalysts have been studied: naphthalene radical anions, supramolecular alkali metal ion pairs, and activated organic anions.

Ring-opening of β-Propio- and β-Butyrolactones *via* Single Electron Transfer.

Reactions between potassium naphthalenide and β-lactones in either in the absence or the presence of 18-crown-6 gave enolates after proton abstraction. The enolates yielded salts of α,β-unsaturated carboxylic acids by ring cleavage (Scheme 1). Abstraction of the α-proton from the lactone by potassium naphthalenide is accompanied by a partial reduction of naphthalene. Thus, the formation of 1,2- and 1,4-dihydronaphthalene (mole ratio = 1:4) was detected by GC-MS. If an excess of β-lactone was used in the reaction catalysed by potassium naphthalenide, polymers were formed (Scheme 1). Some results of the polymerization of β-propiolactone and β-butyrolactone are shown in the Table 1. The experimental procedure is described in reference [4]

The alkali metal naphthalenides, known for efficient reactions with styrene [5,6] and ring-opening reactions with oxiranes [7] and thiranes [8], are able to react with β-propio- and β-butyrolactones [4] *via* single electron transfer in contrast to previous statements [9].

Ring-opening Reactions of β-Butyrolactone *via* Two-electron Transfer.

It is well known that hydrolysis, alcoholysis and acidolysis of four membered β-lactone rings proceed *via* alkyl-oxygen or acyl-oxygen bond cleavage [10]. However, an unprecedented C-C bond scission in the strained β-lactone ring by the potassium metal supramolecular complex K^+,18-crown-6,K^- has been observed recently [11]. These alkali metal supramolecular complexes were discovered by Dye [12] and Edwards [13], who studied the process of potassium (and other alkali metals) dissolution in aprotic solvents, *e.g.* tetrahydrofurane. The preparation of concentrated alkali metal solutions was accomplished in an aprotic solvent containing a crown ether or a cryptand. In contrast to alkali metal solutions in ammonia, the blue solutions of alkali metals in an aprotic solvent contain not only solvated electrons and crowned metal cations but also alkali metal anions. So the previous assumption [14] that an alkali metal can exist in solution as an anion has been confirmed.

The preparation of alkali metal solutions in ethereal solvents is very simple and has been described in detail [12]. Usually, to a potassium mirror or sodium-potassium alloy dispersion in tetrahydrofuran, a complexant, *e.g.* 18-crown-6 or cryptand 222, is added and metal dissolves instantly. Such solutions containing a mixture of solvated electrons, crowned metal cations and metal anions are very active reducers and have been used in organic synthesis. However, the results of their activity were not always reproducible [15]. Kinetic studies have shown that the process of metal dissolution can be rationalized and produces solutions containing only metal anions and complexed metal cations *e.g.* K^-,K^+ crown. Thus, alkali metal ion pairs in solutions can be prepared with concentrations of electrons being very low, and the role of electrons as reagents is in this case negligible [16].

The process of metal dissolution and the composition of the resulting solution was monitored by ESR and alkali metal NMR [17]. So far, the following alkali metal complexes, soluble in ethereal solvents and forming metal ion pairs in solution, have been characterized [18] : K^+/15C5,K^-; K^+/Glyme,K^-; K^+/18C6,Na^- and K^+/18C6,K^- (where 18C6 = 18-crown-6 and 15C5 = 15-crown-5).

The stability of the metal solution depends on the temperature and on the type of ligand used. Potassium or sodium-potassium ion pairs in THF form blue solutions with 18C6 or 15C5, and are stable under an inert gas (*e.g.*, argon) atmosphere at low temperatures. At an ambient temperature of 20 °C, the stability of such solutions is limited, up to several hours.

Alkali metal complexes are important because of their unique metal ion pair structures in solution and their ability to transfer electrons to suitable substrates, a fact that has been utilized in many organic syntheses and catalytic processes. In most cases, K^- and Na^- transfer two electrons from their outer orbital to a substrate to form a carbanion or enolate anion:

$$M^- \xrightarrow[\text{transfer of } 2e^-]{\text{substrate}} M^+ + \text{carbanion}$$

where M=K or Na

In the reaction of 4-membered β-butyrolactone with the alkali metal complex: K^-,K^+crown, the direct evidence for a two electron transfer was provided by ^{39}K NMR. Spectra were taken before the reaction of the potassium complex with β-butyrolactone and after the reaction. As shown in Figure 1 the characteristic K^- NMR signal disappeared after the two electrons were transferred. The reaction mechanism includes an unprecedented C-C bond scission of the lactone ring (Scheme 2).

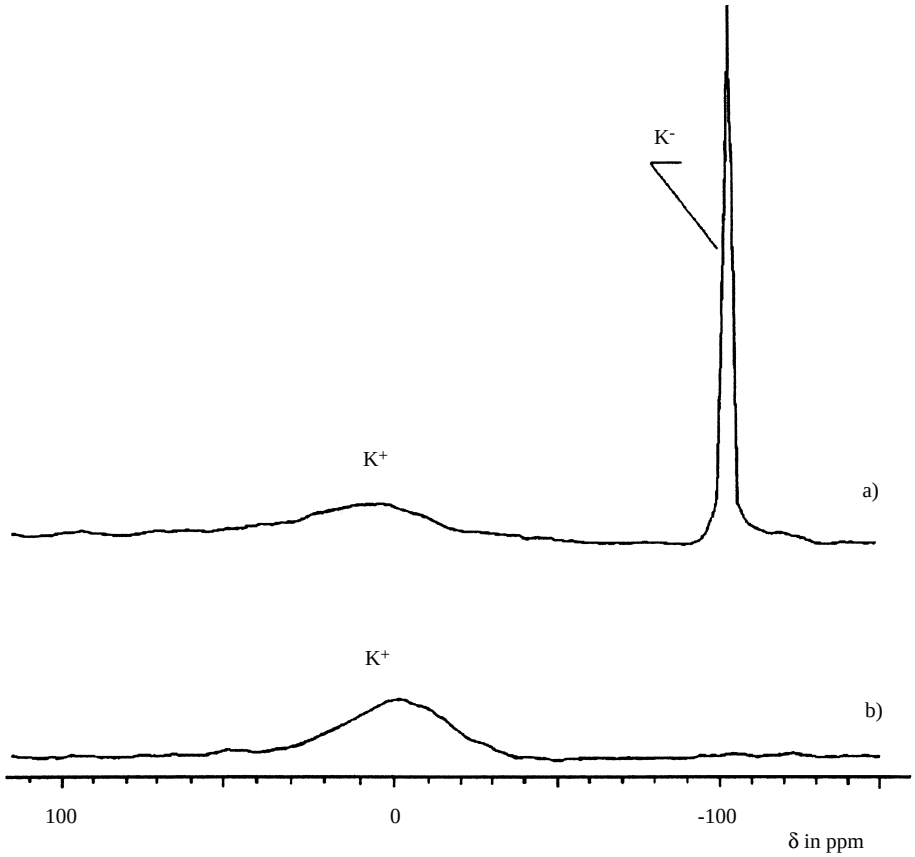


Figure 1. a) ^{39}K NMR of the potassium ion pair with 18-crown-6 in THF solution before a reaction; b) ^{39}K NMR of this solution after a reaction.

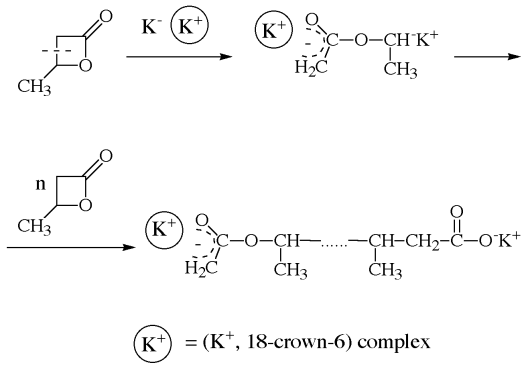
The driving force of this unique C-C bond cleavage is obviously the strong resonance stabilization of the intermediate enolate carbanion. This intermediate carbanion can serve as a useful synthon in various reactions, such as protonation, alkylation and acylation [11,19]. Such course of this reaction is valid for unsubstituted and substituted β-lactones.

It is known that C-C bond scission can occur between aliphatic carbon atoms that bear bulky substituents, *e.g.* arenes, in reactions with alkali metal alloys in a suspension [20], but prior to the work described here, C-C bond cleavage in heterocycles has not been reported. This novel reaction of β-lactones can be applied to organic synthesis and synthesis of polyesters.

Ring Opening Reactions of β-Lactones *via* Nucleophilic Substitution by Activated Anions.

Kinetics of nucleophilic substitution with inorganic anions, *e.g.*, fluorides in organic solvents have been measured as well as under conditions of phase-transfer catalysis (PTC) by many authors [21,22]. However, information is scarce on the ring-opening reactions of β–lactones with activated organic anions.

Scheme 2



In the case of alkali metal alkoxides or carboxylates used in the ring-opening reactions of lactones, anion reactivity depends very strongly on interactions with the surrounding molecules. Cation-anion association and solvent-anion interactions are important factors

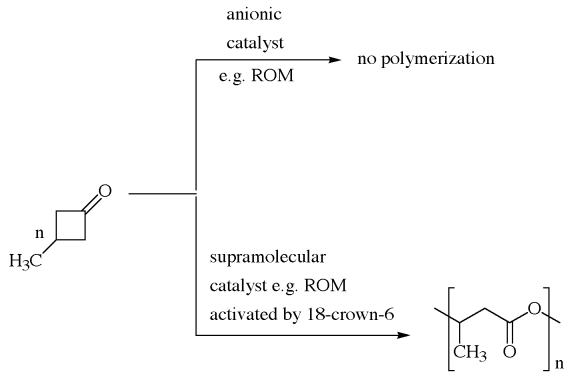
determining anion reactivity. The influence of various solvents on anion reactivity has been studied in many nucleophilic substitution reactions [23].

In homogeneous solutions of anionic species, the following equilibria, where L denotes ligand capable of cation complexation, are important. 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 complexing 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 the bulky complexed cation, and (2) increased anion concentration due to the better solubilization of the reagent (eq 1) [24].

$(M^+A^-)_n$	M^+A^-	$M^+(solv.)A^-$	L	M^+L, A^-	
ion pairs ⟶	contact ⟶	solvent	⟶	loose	(1)
aggregates ⟵	ion pairs ⟵	separated	⟵	ion pairs	
		ion pairs			

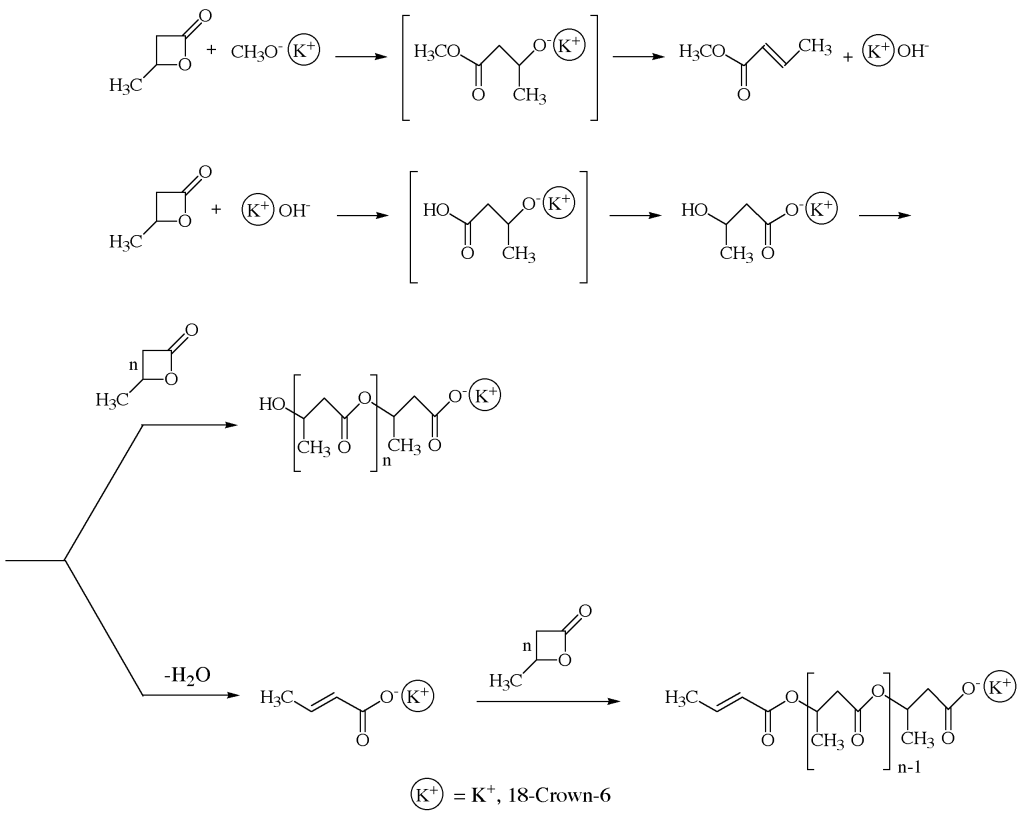
In an attempt to synthesize poly-(*R*)-hydroxybutanoic acid similar to natural PHB present in living systems, we employed activated anions in the polymerization of β–butyrolactone. In these syntheses we employed (*S*)-β–butyro-lactone as the monomer and potassium methoxide or *tert*-butoxide as catalysts. However these attempts failed. The yield of ring-opening of β–butyrolactone could be enhanced only if a crown ether, *e.g.* 18-crown-6, was added and activation of the alkoxide anion occurred due to complexation of potassium cation (Scheme 3)

Scheme 3



where R - alkyl, M = K or Na

Scheme 4



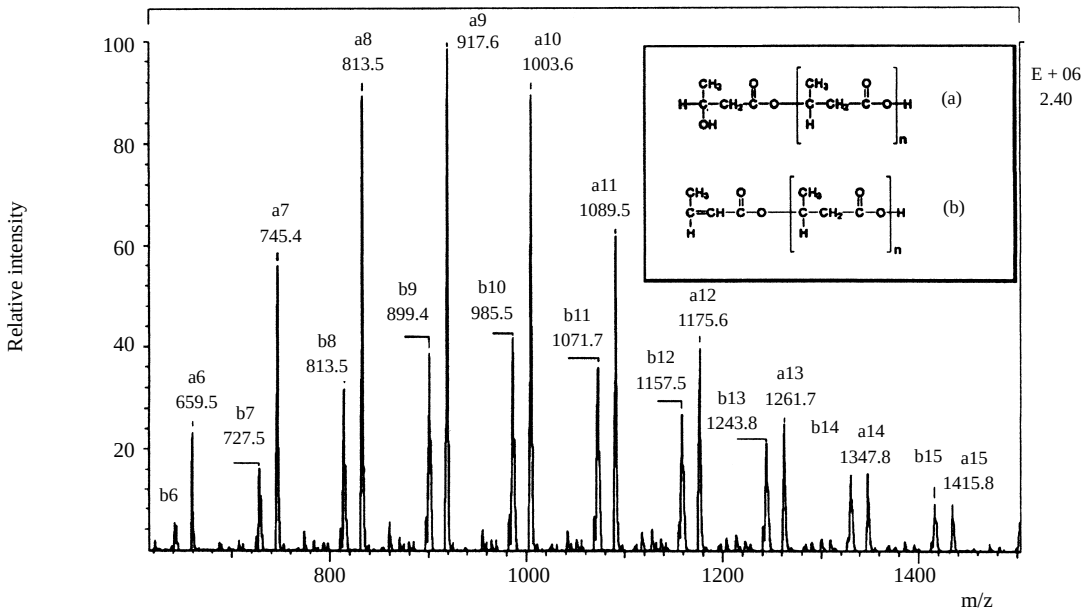
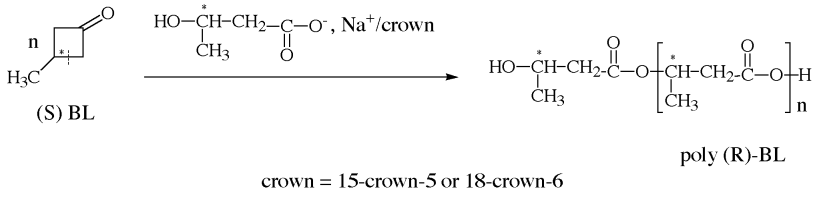


Figure 2. ESI - MS analysis showing two types of polymer structure with different end groups [a and b].

Scheme 5



It turned out that polymerization using (*S*)-β–butyrolactone proceeded regioselectively with inversion of configuration because a substitution-elimination mechanism is operating in this reaction [25]. 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 4), the polymer chains also contain a certain number of unsaturated crotonate end groups as confirmed by ESI-MS analysis (Figure 2). Thus, the structure of the synthetic polymers is similar but not identical to that of the natural PHB polyesters.

The fact that even small structural defects, such as unsaturated crotonate groups, can change the biochemical behaviour of a biopolymer indicates that another regioselective initiator is needed to produce poly-(*R*)-3-hydroxybutanoic acid bearing only the -OH and -COOH end groups present in 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 showed that polymerization of (*S*)-β–butyrolactone with this initiator, performed in bulk or in an organic solvent, proceeded regioselectively with inversion of configuration, and the structure of the obtained polymer is identical to that of the natural biomimetic product [26] (Scheme 5).

The results presented here show the great utility of activated organic anions in ring-opening of β–lactones. Due to nucleophilic substitution, biomimetic oligomers and polymers can be synthesized.

Conclusions.

The great versatility of the ring-opening reactions of β-1actones proceeding *via* electron transfer or nucleophilic substitution with activated organic anions is worth emphasizing. Depending on the nature of a catalyst, its activation and the presence of alkyl substituents in the four-membered β-lactone ring, either alkyl-oxygen and acyl-oxygen or unprecedented carbon-carbon bond-scission can be observed. Supramolecular assistance to the ring-opening reaction of β-lactones is essential. New vistas in supramolecular assistance can be envisioned by the synthesis of novel macrocyclic ligands able to complex a variety of cations [27-30].

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