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Ring-opening polymerization of [beta]-substituted-[beta]-propiolactones :: synthesis of biodegradable polymers and stereochemistry study/

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RING-OPENING POLYMERIZATION OF ß-SUBSTITUTED-ß-PROPIOLACTONES: SYNTHESIS OF BIODEGRADABLE POLYMERS AND STEREOCHEMISTRY STUDY

A Dissertation Presented

By

YAN ZHANG

Submitted to the Graduate School of the
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Polymer Science and Engineering

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Robert W. Lenz, Chairman

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William E. McEwen, Member

W.J. MacKnight, Department Head
Polymer Science and Engineering

Dedicated to my husband, Li Dong

and my daughter Angela.

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ABSTRACT

RING-OPENING POLYMERIZATION OF ß-SUBSTITUTED-ß-PROPIOLACTONES: SYNTHESIS OF BIODEGRADABLE POLYMERS AND STEREOCHEMISTRY STUDY

SEPTEMBER, 1990

YAN ZHANG, B.S., BEIJING UNIVERSITY

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Directed by: Professor Robert W. Lenz

Biodegradable polymers, for biodegradable plastic utility and drug release biomedical applications, are the primary objectives of this theses research. We have synthesized poly(ß-hydroxybutyrate) (PHB), poly(ß-malic acid) (PMA) and their copolymers by the ring-opening polymerization reactions of ß-butyrolactone and ß-benzyl malolactonate. A varity of catalysts were used, including the stereoregulating catalysts, ethyl aluminoxane (EAO) and the product of the in-situ preparation of Et_3Al/H_2O, as well as the non-stereoselective catalysts, Et_2Zn/H_2O and (5,10,15,20-tetraphenylporphinato)aluminum chloride (TPPAlCl).

The degree of stereoregulation of the homopolymers was enhanced by the use of a stereoregulating catalyst, followed by product extraction. The resulting insoluble fractions of PHB and PBML are stereoregular crystalline polymers having high molecular

weights, with the former compared with naturally occurring P([R]-HB) in corresponding properties. The stereoregularity of the synthetic polymers was determined by ^{13}C (75.4 MHz) NMR spectroscopy, differential scanning calorimetry (DSC) and FTIR spectroscopy. The yield of polymerization was optimized by using the Et_2Zn/H_2O and TPPAlCl catalysts, resulting the amorphous polymers with relatively low molecular weights. The analysis of copolymer tacticity and comonomer sequences by using ^{13}C-NMR and DSC indicats a random distribution of the copolymer sequences.

The stereochemical couse of the ring-opening polymerization of BL with the Et_3Al/H_2O and Et_2Zn/H_2O catalysts was studied using [S]-BL as a stereochemical probe. The [S]-ß-BL, which was prepared in five steps from naturally occurring P([R]-HB), had an optical purity in excess of 97% as measured by ^1H NMR spectroscopy in the presence of a chiral europium shift reagent, $Eu(hfc)_3$. The stereochemical configuration and isomeric purity of the repeating units in the polymers obtained were determined both from their specific optical rotation and by degradation of the polymers to their component methyl ß-hydroxybutyrate units. From our investigations it was concluded that the ring-opening reaction can be carried out by different routes in the Al- and/or Zn-water catalysts, and the two enantiomers, P([R]-HB) and P([S]-HB) were obtained as the result of the configuration retention or inversion. These enantiomers of PHB are very useful for the study of the stereochemistry of synthetic poly(ß-lactone)s and their biodegradability.

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INTRODUCTION

1.1 Biodegradable Polymers

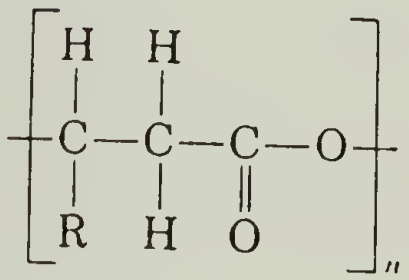
A biodegradable polymer is a macromolecule which can be broken down by the activity of living organisms.[1] The biodegradation of synthetic polymers can occur under physiological conditions with water, catalyzed by hydrolytic enzymes or under enviromental conditions where the presence of oxygen in air, soil and sea-water are conducive for the action of microorganisms.[2] Biodegradable polymers can be used as plastic containers and packaging, in agriculture, and for medical applications such as drug delivery systems. In the application of biodegradable polymers, especially for in-vivo biomedical uses, neither the polymer nor the small molecules resulting from polymer degradation should be toxic or antigenic, and the degraded products must be either easily metabolized or readily excreted.

Synthetic biodegradable polymers have been the focus of a lot of attention in recent years mainly because of the problem in waste disposal of plastics and the demand for controlled drug delivery systems.[3-4] One of the advantages of synthetic biodegradable polymers over those produced from bacteria is that one can have greater control over the chemical composition and physical properties of the material.[5] Polyesters are mostly studied in this field because they are usually hydrolytically degradable at the ester group, and also because of the chemical and physical

properties such as thermoplasticity and crystallinity, which can be controlled by varying the composition.[6-8]

1.2 Polyesters Studied

ß-substituted poly(ß-propiolactone)s, with the repeat unit shown below, represent an interesting series of polyesters.



The best known example of this series is poly(ß-hydroxybutyrate) (PHB) in which R=CH_3. This polymer is found in bacteria[9] as a carbon and energy storage material.[10] Naturally occurring PHB is synthesized in the cell by the condensation of D-(-)-ß-hydroxybutyryl coenzyme-A (Figure 1.1),[11] and the polymer is subsequently enzymatically converted to ß-hydroxybutyric acid, which is a metabolite in the fatty acid ß-oxidation cycle. This polymer, therefore, is inherently biodegradable in environments such as soil, anaerobic sewage, and sea-water.[12] Recently considerable attention has been paid to the synthesis of this type of polyesters from both racemic and optically active lactones,[13-14] especially with regard to the stereoregular polymerization[15-19] of this type of lactone.

We are interestd in the synthesis of a functional copolyester containing an HB unit and an unit from benzyl malolactonate (BML),

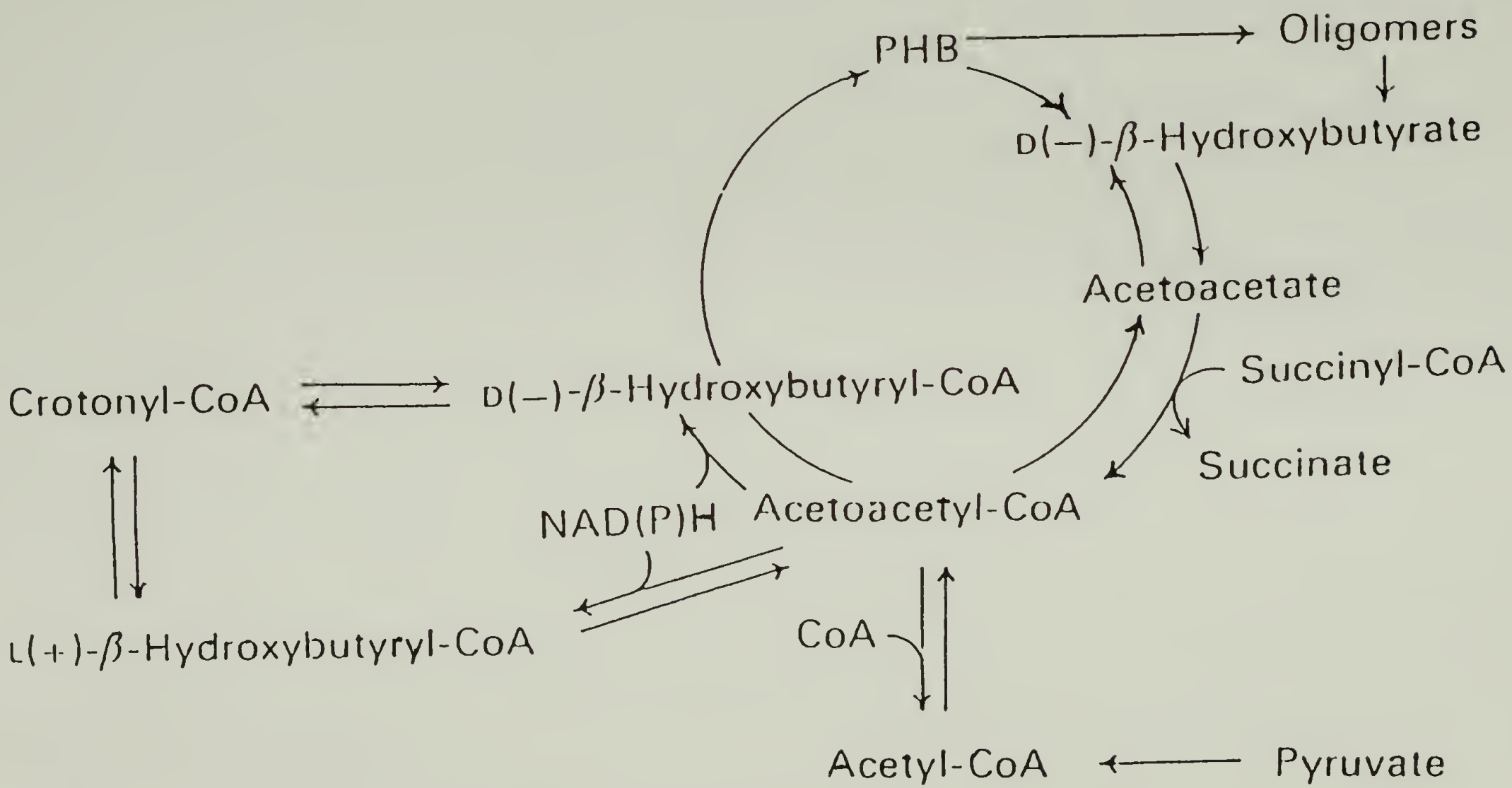


Figure 1.1 Synthesis and degradation of bacterial poly(β-hydroxybutyrate) (PHB).

in which the ß-substituents are methyl and carboxy benzyl groups ($R=CH_3$, $COOCH_2C_6H_5$), respectively. We believe that there is a high potential for commercial applications of the polyester as a biodegradable functional material.[20-22]

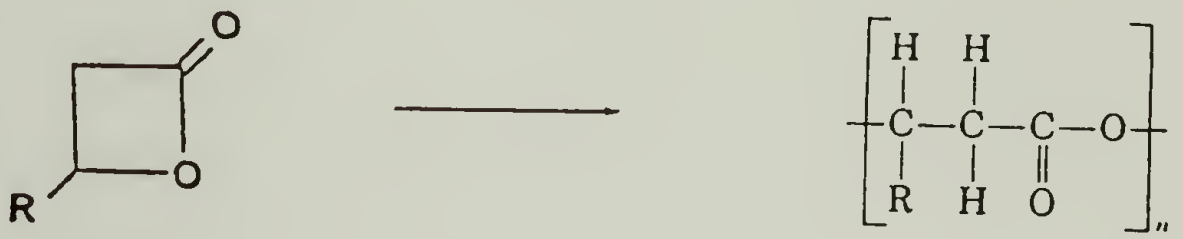
Naturally occurring PHB is 100% isotactic because the chain chiral center of each repeating unit has only a R configuration.[10,23] It is highly crystalline after extraction, and it crystallizes in a 2_1 helical conformation.[19] It was found that PHB has broad similarities at the structure and physical properties to isotactic polypropylene,[29] which, like PHB, has a helical crystalline conformation and a melting point close to 180°C. The thermoplasticity of PHB, in combination with its biodegradability, has focused attention on biodegradable fiber and plastics applications of this polymer.

Synthetic PHB prepared from ß-butyrolactone can also be referred to as poly(ß-butyrolactone) (PBL). The main object of PBL homopolymerization from both racemic and optically active ß-BL, in this study, was to establish the nature and preparation of catalyst which can give a stereoregular polymer having a high molecular weight to compare with the naturally occurring PHB, and to extend our knowledge of the mechanism of the ring-opening reaction by which this polymerization occurs. The special interest in the PBML ($R=COOCH_2C_6H_5$) is that it can readily be debenzylated[20-21] without degradation[43-47] to form poly(malic acid) (PMA) (R=COOH), which has a functional group (carboxylic acid). Furthermore, the hydrolysis product of PMA is malic acid

(MA) which is an intermediate in Krebs cycle and consequently, nontoxic.[48] Thus, this functional polymer could served as an ideal biodegradable material as a drug delivery carrier.[44-46]

1.3 Ring-Opening Polymerization of ß-Substituted-ß-Propiolactones

The ring-opening polymerization of ß-substituted-ß-propiolactone is known to give the poly(ß-hydroxyalkanoates), PHA, shown below:[23]



1.3.1 Ionic Polymerization

Attempts[24-28] were made to synthesize P[R,S]-HB, or PBL, from racemic ß-butyrolactone (BL) by using cationic or anionic initiators and catalysts.

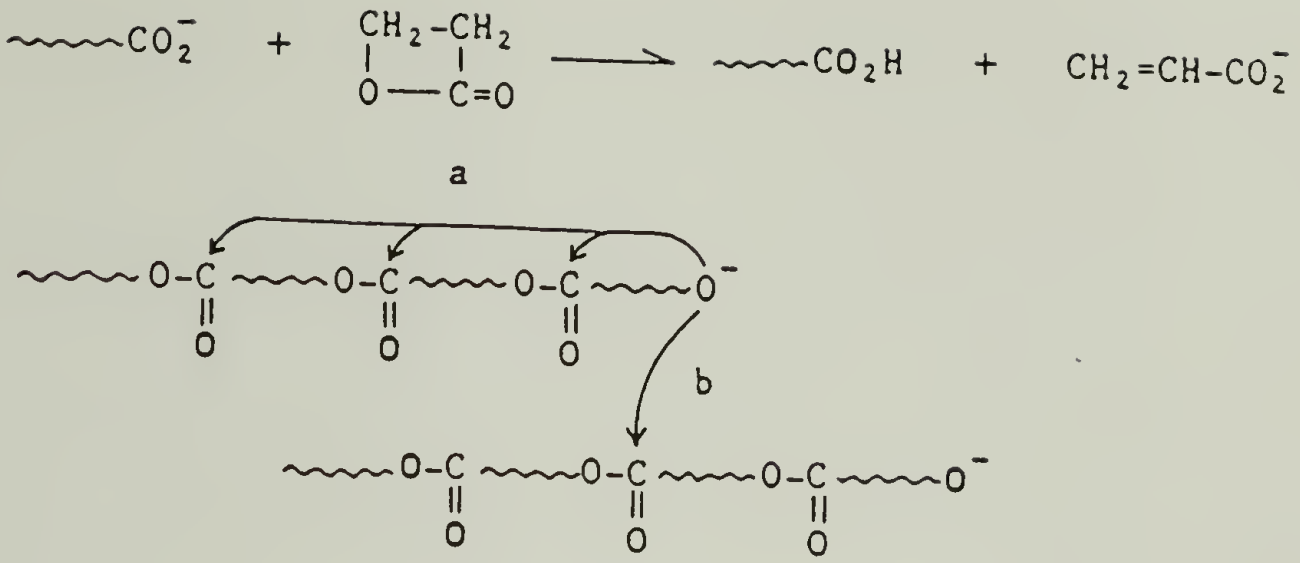
Although various acidic compounds were reported by Kricheldorf and coworkers[24-25] to be initiators for the cationic polymerization of glycolide and L,L-dilactide, only a few of them can be used in the polymerization of ß-substituted-ß-propiolactone because of chain transfer and termination reactions.[15-16] With cationic catalysts, (e.g., BF_3-OEt_2 and $SnCl_4$), raemic ß-lactones substituted with methyl, ethyl, i-propyl and t-butyl groups at the ß-position gave atactic polymers of relatively

low molecular weights in high yields.[16] These results suggest that the substituted group in the monomer has little effect on both the stereochemistry and rate of the ring-opening reaction for such catalysts. However, chain transfer and termination reactions with counter-ions and impurities could not be avoided when using cationic catalysts for the lactone polymerization.

For anionic initiators, the polymerization of ß-substituted-ß-propiolactone was previously considered unfavorable because of the likelihood of both proton abstraction at the active α-C-H group of the monomer and the intra- and intermolecular transesterification reactions, as shown in Figure 1.2-a.[26] The abstraction reaction could lead to the formation of an α,ß-unsaturated carboxylic acid, and the two latter reactions would lead to the formation of cyclic oligomers and polymers with multiple molecular weight distributions. In a recent study by Jedlinski and coworkers,[27-28] however, potassium solutions were found to be active initiators in the ring-opening polymerization of ß-substituted-ß-propiolactones. The initiation step proposed by them involved an unusual scission of the C_α-C_β bond at the lactones with H, CH_3, and C_2H_5 ß-substituents, as shown in Figure 1.2-b. However, only low molecular weight polymers were produced from the polymerization of ß-BL by this anionic procedure.[27-28]

The polymerizations of benzyl malolactone (BML) in both racemic[42] and enantiomerically pure forms[43-45] have been previously carried out in this laboratory by using an anionic initiator, tetraethylammonium benzoate. The amorphous polymers

a.



b.

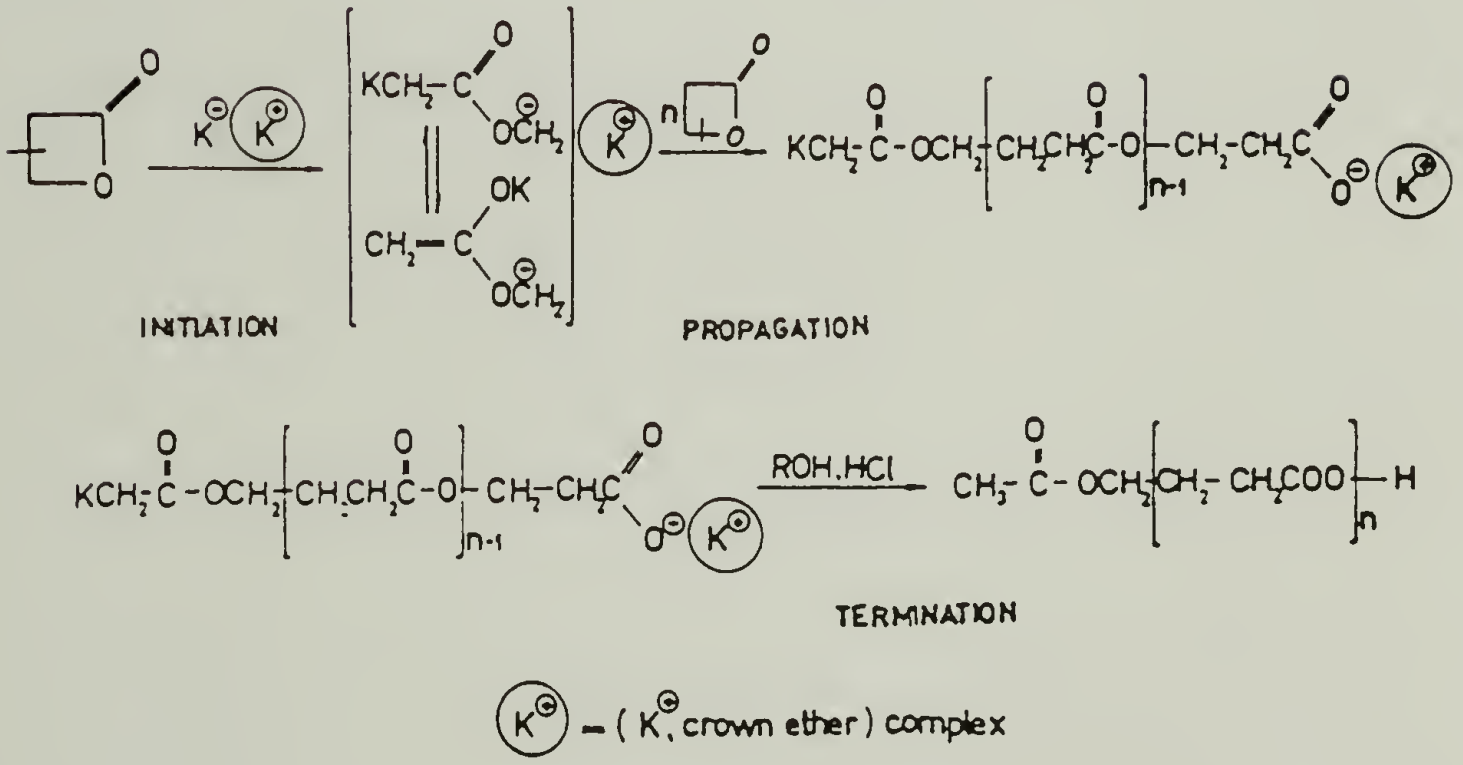


Figure 1.2 Anionic polymerization of β-butyrolactone.
(a) α-proton abstraction and the chain transfer reactions;
(b) the ring-opening polymerization by potassium solution.

synthesized from the racemic monomer were obtained in about 60% yield with a weight average molecular weight, $\bar{M}_w$, of approximately 20,000. The varied yields and molecular weights were observed from batch to batch, and this phenomenon was consistent with the hypothesis that low molecular weight polymers were formed because of chain transfer and/or termination reactions in the presence of small amounts of reactive impurities. In fact, sometimes the crude BML polymerized during its distillation, probably initiated by some impurity. The number average molecular weights, $\bar{M}_n$, of these "thermally" produced polymers were between 3,000 and 5,000.[42]

The polymer formed by using the above initiator, from enantiomerically pure [R]-BML, was obtained in about 85% yield and was crystalline. This polymer had a ΔH_m of 12.5 cal/g and a peak melting temperature of 190°C as determined by differential scanning calorimetry (DSC). The molecular weight determination by gel permeation chromatography (GPC) for this optically active polymer gave values for $\bar{M}_w$ of approximately 100,000 and for $\bar{M}_w/\bar{M}_n$ of 2.1.[43-44]

1.3.2 Coordination Polymerization

An attempt at preparing crystalline PHB from the racemic BL was carried out by using the coordination catalyst, obtained from the reaction of triethylaluminum with water ($AlEt_3/H_2O$), which was previously reported by Araki, Tani and coworkers[15-16] for use in a variety of polymerization reaction of polar monomers.[29-32]

The P(HB) polymer obtained with this aluminum-based catalyst had a high molecular weight and a moderate stereoregularity.[15-18] The behavior of the catalyst was found to vary with the ratio of water to $AlEt_3$, presumably because of changes in the predominat species of organoaluminum oxide.[15-16,32-33] The highest catalytic activity with respect to stereospecific polymerization was obtained at a ratio of $AlEt_3$ and H_2O of 1:1.

More recently, attention has been directed toward the catalyst ethylaluminoxane (EAO), which is believed to be a oligomer of the structure: $-(-AlEtO-)_n-$.[16,34] This catalyst appears to be more stereoregulating, to have better catalytic activity, and to exhibit an improved reproducibility for the polymerization of ß-BL. EAO has also been used to polymerize a variety of ß-alkyl and ß-chloroalkyl-ß-propiolactones,[4] and it is even active for monomers in which the ß-substituent is an ester functionality.[35-36] The methyl aluminoxane (MAO), $-(-AlMeO-)_n-$, has also led to much interest as a catalyst in Ziegler-Natta polymerization reactions.[37-39] It was reported that an extremely active, soluble catalyst can be obtained by mixing Cp_2ZrCl_2 or $Cp_2Zr(CH_3)_2$ with MAO, and the resulting catalyst has an improved effect in the stereospecific polymerization of propylene.[38]

Another type of coordinate anionic catalyst, bimetallic μ-oxoalkoxide such as $(n\text{-}C_4H_9O)_4Al_2O_2Zn$, has been reported recently to catalyze the stereoregular polymerization of lactones.[40] Living polymers with narrow molecular weight distributions were obtained with this catalyst for poly(ϵ-caprolactone), poly(γ-

valerolactone) and poly(ß-propiolactone) under mild conditions.[41] However, this catalyst was not sutible for ß-BL because the intermediate polyester thermally decomposed in the presence of the catalyst into the corresponding unsaturated 2-butenoic acid.[41]

The $Et(ZnO)_2ZnEt$ catalyst, which is derived from the reaction of $ZnEt_2$ with H_2O, was found to be effective for the synthesis of high molecular weight atactic PBL.[15-16] Thus, it is possible using this Zn- and the Al-catalyst to obtain the properties of either the stereoregular polymers (produced with the $AlEt_3/H_2O$ catalyst) or the corresponding atactic amorphous polymers, especially with regard to the effect of stereochemistry on properties.

Both the $AlEt_3/H_2O$ and $ZnEt_2/H_2O$ catalysts are reported to be coordinative in character. This kind of catalyst is mostly often used for polymerization of ß-substituted-ß-propiolactone because of its success in obtaining high molecular weight polymers.

In this work, the ring-opening polymerization of ß-BL and ß-BML was studied by using several different coordination catalysts, especially the alkylaluminoxanes, including EAO, MAO and IBAO (isobutylaluminoxane) to synthesize crystalline PHB, PBML and their copolymers, P(BM-co-HB). The polymeric products obtained from these cataltsts were fractionated and characterized by ^{13}C NMR, Fourier transfer infrared (FTIR) spectroscopy and DSC to determine the relative abilities of these catalysts to synthesize stereoregular polymers. The diethylzinc-water, $ZnEt_2/H_2O$, (1:0.6) catalyst and (5,10,15,20-tetraphenylporphinato)aluminum chloride (TPPAlCl) were also used in this study, especially in the

copolymerization of ß-BL and BML.

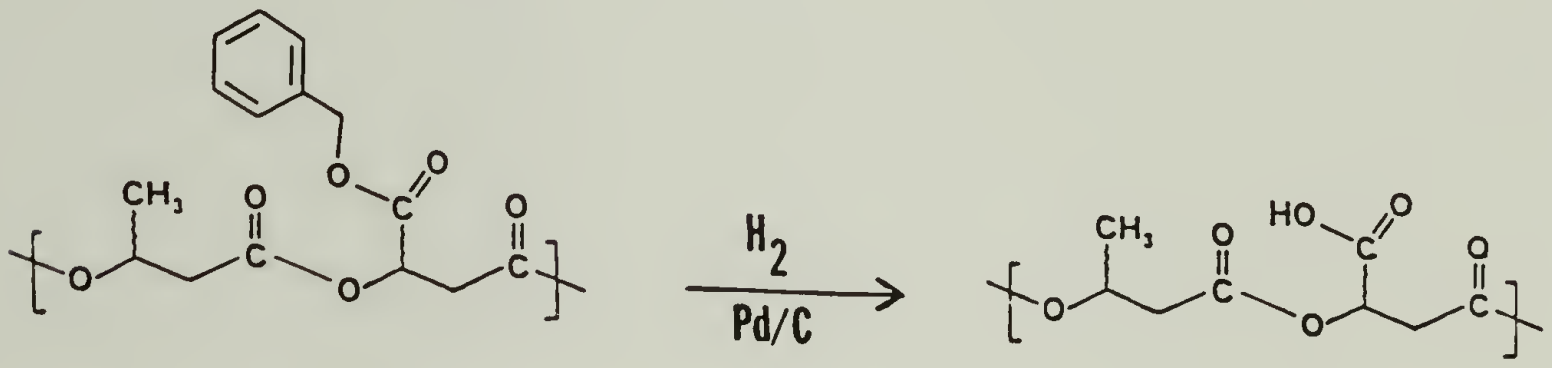
1.4 P(HB-co-HV) Copolymers

Because of its perfect stereoregularity, naturally occurring PHB is a highly crystalline material, but its ß-substituted structure makes it thermally unstable at temperatures not far above its melting point of 179°C,[49] and both of these characteristics pose potential difficulties in the use of this polymer for plastics and fibers. However, these disadvantages can be overcome by copolymerizing BL with other lactones to decrease the melting point and improve the physical properties, such as toughness and flexibility. A random copolyester containing ß-hydroxybutyrate and ß-hydroxyvalerate (R=CH_3, CH_2CH_3) units, P(HB-co-HV), produced by ICI is one of such products.[50-51] The first of this type of synthetic copolyester was prepared by Marchessault and Bloembergen using the $AlEt_3/H_2O$ catalyst.[52] The copolymer obtained was highly crystalline because of the isodimorphic properties of the two repeating units.[52] The NMR analysis indicated that two units present were in a random distribution, presumably because BL and VL have very similar reactivites.[53]

1.5 Functional Copolymers, P(HB-co-BML)

A functional copolyester containing the HB unit and the unit from ß-malolactonate BML, as shown below, was prepared in this study. This copolymer is of special interest in the PBML unit

because it can readily be debenzylated without degradation to form poly(malic acid) (PMA), as shown below, which has a functional group (carboxylic acid) available for coupling reactions with some interesting materials.



P(HB-co-BM) P(HB-co-MA)

These P(HB-co-MA) copolymers can have variable degrees of carboxylic acid functionality, and therefore, hydrophilicity, according to the monomer feed and the relative reactivities of BL and BML. By varying the ratio of the comonomer units, the biodegradability as well as the physical and mechanical properties of the copolyesters can be controlled. All of these characteristics of the copolymers could generate several potential applications for these biodegradable polyesters including their use as thermoplastics, fibers and biomedical applications.

1.6 Biomedical Applications

The biological property of amorphous poly([R,S]-malic acid), PMA, has been reported by Vert and coworkers.[48] PMA was shown to be degraded into malic acid under physiological conditions. When

the polymer was dissolved in a phosphate-buffered saline solution of pH 7.5, changes in molecular weight were followed by GPC measurement, and [S]-malic acid was detected by an enzymatic reaction. The half-life in terms of molecular weight loss (that is, the time required to reduce the molecular weight by fifty percent) was determined at three different temperatures. At 50°, 37° and 25°C, the half-lives for the degradation were 10, 110 and 560 hours, respectively.

These hydrolysis data demonstrated two complementary properties of PMA. Firstly, PMA degraded into its nontoxic monomer, malic acid, and secondly, PMA degraded slowly enough to be used as a polymeric drug carrier. Furthermore, PMA was also shown to be relatively nontoxic and nonantigenic.[54] In one study, no mice died after being injected with racemic PMA so that no LD50 was calculated. In another study, a low acute toxicity was reported,[43-44] in that immune response (antibody generation) was detected against racemic PMA, although this observation may be the result of the use of low molecular weight polymers and the short exposure time of the polymer.

Little research has been done on the biodegradability of racemic P(HB) in either environmental or physiological situations. Racemic P(HB), in the form of a stereoblock copolymer, showed some ability to biodegrade enzymatically under environmental conditions, because at least part of the polymer can be identified with the naturally occurring PHB, in stereostructure, but nothing is known about the biodegradability of the non-natural P(HB) isomer.

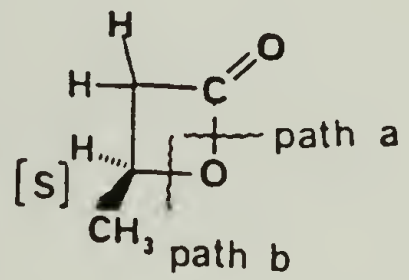
It is known that the morphology of a polymer has an influence on its degradability under physiological conditions. Amorphous polymers are generally much easier to be degraded than crystalline polymers because of the solubility and accessbility differences. As already mentioned, the copolymer P(HB-co-MA) can have a varible hydrophilicity by changing the ratio of MA to HB, so this copolymer can be soluble under physiological conditions when it has a high enough content of the hydrophilic MA units, and it should readily degrade into ß-hydroxybutyric acid and malic acid because the polymer has hydrolyzable ester linkages. It was found that the P(HB/MA) copolymer obtained by a different catalyst in this study has a comonomer distribution close to random and is amorphous. The degradability, solubility and varible functionality in combination with the metabolism of the copolymer should make it of potential use in drug delivery systems.

1.7 Stereochemistry of the Ring-Opening Polymerization of the ß-Lactone

The mechanism of stereoregulation in the polymerization of ß-lactones is a subject for which little definitive information is available. As mentioned previously, the major difference between the catalytic properties of the AlR_3/H_2O and ZnR_2/H_2O catalysts for lactone polymerization is that the Al catalyst gives stereoregular polymers whereas the Zn catalyst produces, without exception, non-stereoregular polymers,[53-56] but to date little is known about the molecular basis for the apparent stereoregulation

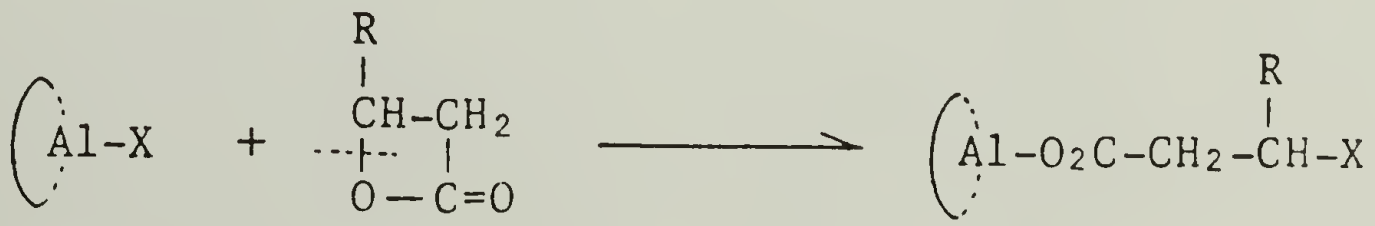
in these ring-opening polymerizations.

The ring opening polymerization of ß-substituted-ß-propiolactone may proceed by bond breaking between either the acyl carbon and oxygen (path "a"), or the alkyl carbon and oxygen (path "b"), as shown below.



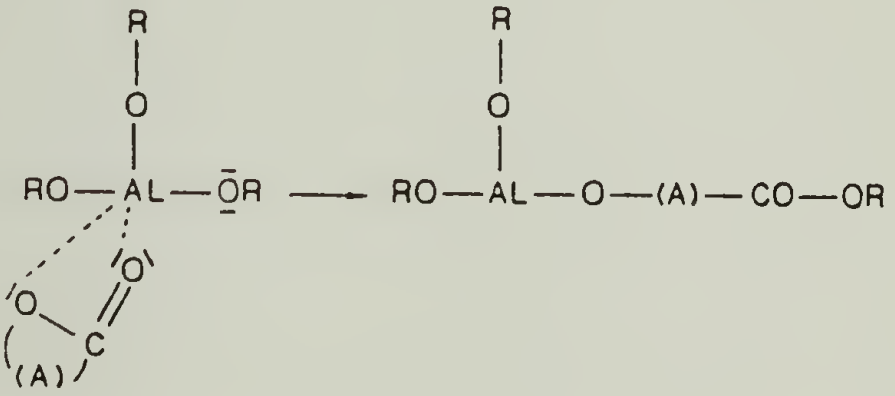
The differentiation between the propagation involving path "a" or path "b" is difficult to achieve by kinetic methods, but the true pathway can be ascertained either by end-group analysis (living polymerization systems[57-59]) or by polymerization of an enantiomeric monomer.[60-63]

The living polymerization of ß-propiolactone and ß-butyrolactone using the initiator TPPAlCl was reported by Inoue and coworkers.[57-59] The analysis of the "living end" using ^1H NMR spectroscopy indicated that only the (porphinato)-aluminum carboxylate was present. In that case, therefore, the ring cleavage must occur at the alkyl-oxygen bond (path "b"), as shown below.



TPPAlCl

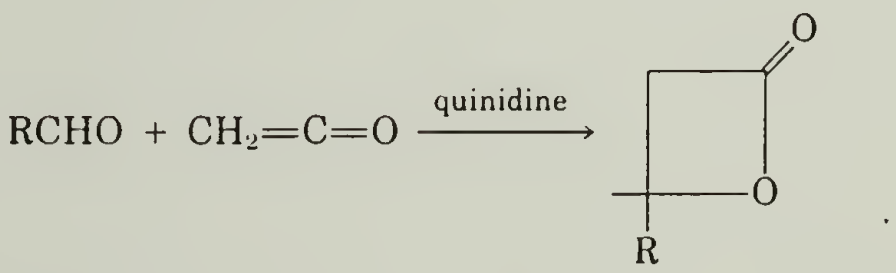
Recently, Kricheldorf and coworkers revealed a mechanism of the metal alkoxide initiated polymerization of various lactones, including ß-propiolactone and ß-butyrolactone.[59] The initiators used were aluminum isopropoxide and zinc or titanium n-butoxide, among others. From both ^{1}H NMR and ^{13}C NMR spectra, they concluded that in all cases the same initiation and propagation reactions took place. The ring-opening of lactones involved cleavage of the acyl-oxygen bond, and the alkoxide initiator formed alkyl ester end groups, as shown below. The living character, with regard to end-group activities, was also proven in this system.



Unforturnately, this technique for end-group analysis is not suitable for the AlR_3/H_2O and ZnR_2/H_2O catalyst systems because of two reasons. Firstly, the exact nature of the active centers in these catalysts is not clear. Secondly, it is very difficult to produce a polymer with a low enough molecular weight such that the chemical structure of the end group can be analyzed by ^{1}H NMR spectroscopy. In contrast, the optical activity of the polymers obtained in the polymerization reactions from one of the enantiomers is an useful tool for the study of the stereochemistry mechanism.

A mechanistic study of the ring-opening polymerization of ß-BL with the $AlEt_3/H_2O$ catalyst was initially carried out by Shelton and coworkers.[60-61] The monomer used in their work had an optical purity of 73% ee (enatiomeric excess) in [R]-configuration. The resulting polymer had an optical purity close to 40% ee. From a comparison of the chiroptical properties of the synthesized polymer to that of natural origin, P([R]-HB), they concluded that the mode of ring-opening proceeded by acyl-oxygen bond cleavage, path "a", with retention of configuration, but the specific ring-opening mechanism could not be determined clearly because of the low optical purity of the monomer.

Prud'homme and coworkers studied the synthesis and polymerization of optical active chlorosubstituted ß-alkyl-ß-lactones of different optical purities.[62-63] Optically active ß-triflоromethyl-ß-propiolactone (CCl_3-PL) and ß-dichloroethyl-ß-propiolactone (CH_3CCl_2-PL) were obtained by the reaction of ketene with chloro aldehydes in the presence of a chiral catalyst, as shown below:



R = CCl_3 or CH_3CCl_2

Polymerization reactions were carried out in either bulk or in

toluene, at 60° or 80°C, using organometalic catalysts including $AlEt_3/H_2O$ and $ZnEt_3/H_2O$. The polymers became insoluble and crystalline at enantiomeric excesses over 80% for (Cl_3-PL) and 70% for (CF_3,Me-PL). Although the polymers synthesized were optically active, the mechanism of the ring-opening polymerization could not be determined in the absence of the corresponding standard polymers of known optical activity. In contrast, in the present study, the availability of natural origin P([R]-HB) of known charolity, as a standard polymer, makes the study on the mechanism of polymerization of ß-butyrolactone possible.

In this study, a new synthetic route for obtaining highly optically pure [S]-butyrolactone ([S]-BL) was developed by using natural P([R]-HB). The [S]-BL so obtained was used as a stereochemical probe to determine the mode of the ring-opening reaction with the Al- and Zn- catalysts. The optical rotations of the polymers synthesized from [S]-BL were then compared to that of natural P([R]-HB)'s to determine the predominant stereochemical configuration in each polymer. The optical purities of the polymer samples were studied through their corresponding methyl ß-hydroxybutyrate (MHB) stereoisomers, which were obtained by acidic catalyzed methanolysis of the polymers. The optical purities of these MHBs were determined by ^1H NMR spectroscopy in the presence of a shift reagent. The isotactic and syndiotactic diad sequences of the P(HB)s were also determined by ^{13}C NMR spectroscopy, which could be easily resolved for quantitative determination of polymer stereochemical sequence distribution.[64]

A particularly important aspect of the present study is to understand the stereochemical control of the ring-opening polymerization in order to obtain polymers with the desired stereochemistry. These synthetic analogues of natural PHB can be very useful for studying the physical properties and biological activities of bacterial polyesters, which, in many cases, are produced only as copolymers in a limited range of compositions. The polymerization methods developed in this study, therefore, can be used to synthesize homopolymers with a desired stereochemistry which is not currently available from the biosynthetic route.

In summary, there are two goals in this study about the mechanism of the ß-butyrolactone ring-opening polymerization. The first one is to synthesize the stereoisomers of P([R]-HB), P([S]-HB) and the racemic polymer, P([R,S]-HB), for the study of their biodegradabilities as compared to that of natural origin PHB's. The second goal is to understand the stereochemical courses of the ring-opening polymerization reactions with the Al- and Zn-based catalyst systems.

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CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis and Characterization of Racemic Polyesters

2.1.1 Synthesis of Benzyl Malolactonate (BML)

The synthetic route to benzyl malolactonate in this study, which was previously used by Vert and Lenz,[1-5] is shown in Figure 2.1. The overall yield of the ß-lactone based on bromosuccinic acid was 25%.

Bromosuccinic anhydride was synthesized from bromosuccinc acid by a reaction with acetyl chloride. Removal of the by-products under vaccum (10-20 mm Hg) at a temperature under 100°C prevented the formation of malic anhydride, which can be formed by dehydrohalogenation of bromosuccinic anhydride during the distillation.[6] The final yield of bromosuccinic anhydride was increased from 80 to 95%.

The preparation of benzyl bromosuccinate was accomplished by alcoholysis of bromosuccinic anhydride with benzyl alcohol. Slow addition of the alcohol to the anhydride to a final 1:1 molar ratio produced only the monobenzyl bromosuccinate. The reaction was readily followed by IR spectroscopy by monitoring the disappearance of the anhydride doublet at 1800 and 1870 cm^{-1} (IR spectrum #1) and the subsequent formation of a peak at 1750 cm^{-1}, which represents a carboxylic acid and ester carbonyl stretching frequency (IR #2). Analysis of the benzyl

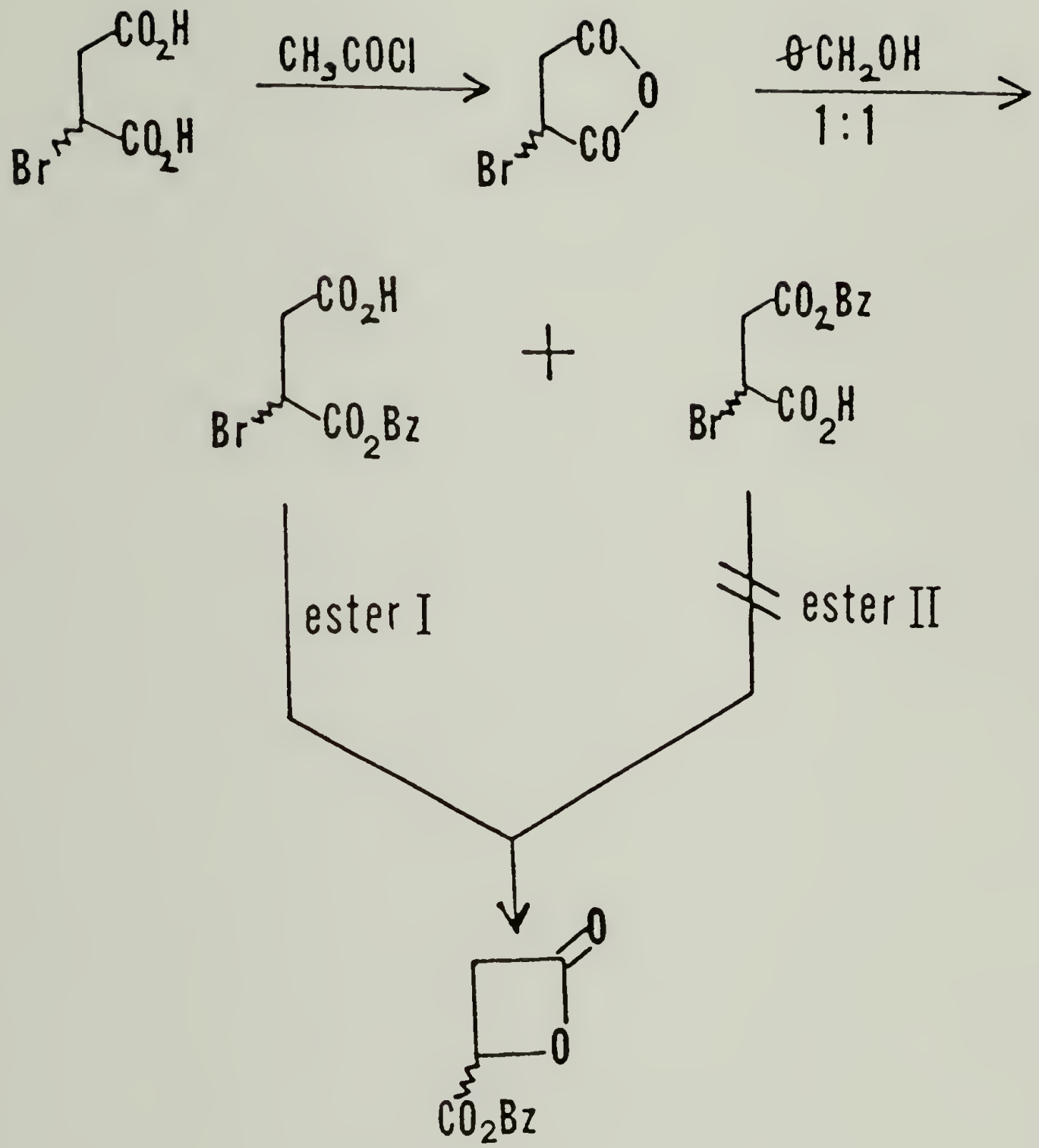


Figure 2.1 Synthesis of racemic benzyl malolactone (BML).

bromosuccinate by ^{1}H NMR and ^{13}C NMR spectroscopy revealed that a 70:30 mixture of the two esters (I:II)[4] was obtained (see Fig. 2.1). The larger amount of ester (I) relative to ester (II) most likely resulted from the enhanced reactivity of the carbonyl group alpha to the bromine to nucleophilic attack by benzyl alcohol because the bromine atom has an electron-withdrawing inductive effect.[7]

Synthesis of the benzyl bromosuccinate by other methods may produce even higher percentages of ester (I), including (a) the direct esterification of bromosuccinic acid, but maintaining an exact stoichiometry and driving the equilibrium toward the desired product would be more difficult than is the corresponding anhydride alcoholysis, and heating to remove water to drive the reaction could result in dehydrohalogenation; (b) conversion of the acid to bromosuccinyl chloride followed by reaction with benzyl alcohol would most likely be less selective than the alcoholysis of the anhydride because acyl halides are much more reactive than anhydrides;[8] (c) addition of hydrogen bromide to benzyl malate, as shown in Figure 2.2, which has been found to lead to a higher percentage (95%) of ester I when the addition was carried out using dry HBr and ether as solvent for the reaction.[9] The selectivity observed in the last case was undoubtedly due to protonation of the carbonyl group of the acid function producing a more stable intermediate.[9] Another complication with the system was the formation of benzyl bromide which interfered with the purification of the product.[4] None of these three reactions were investigated for the reasons given.

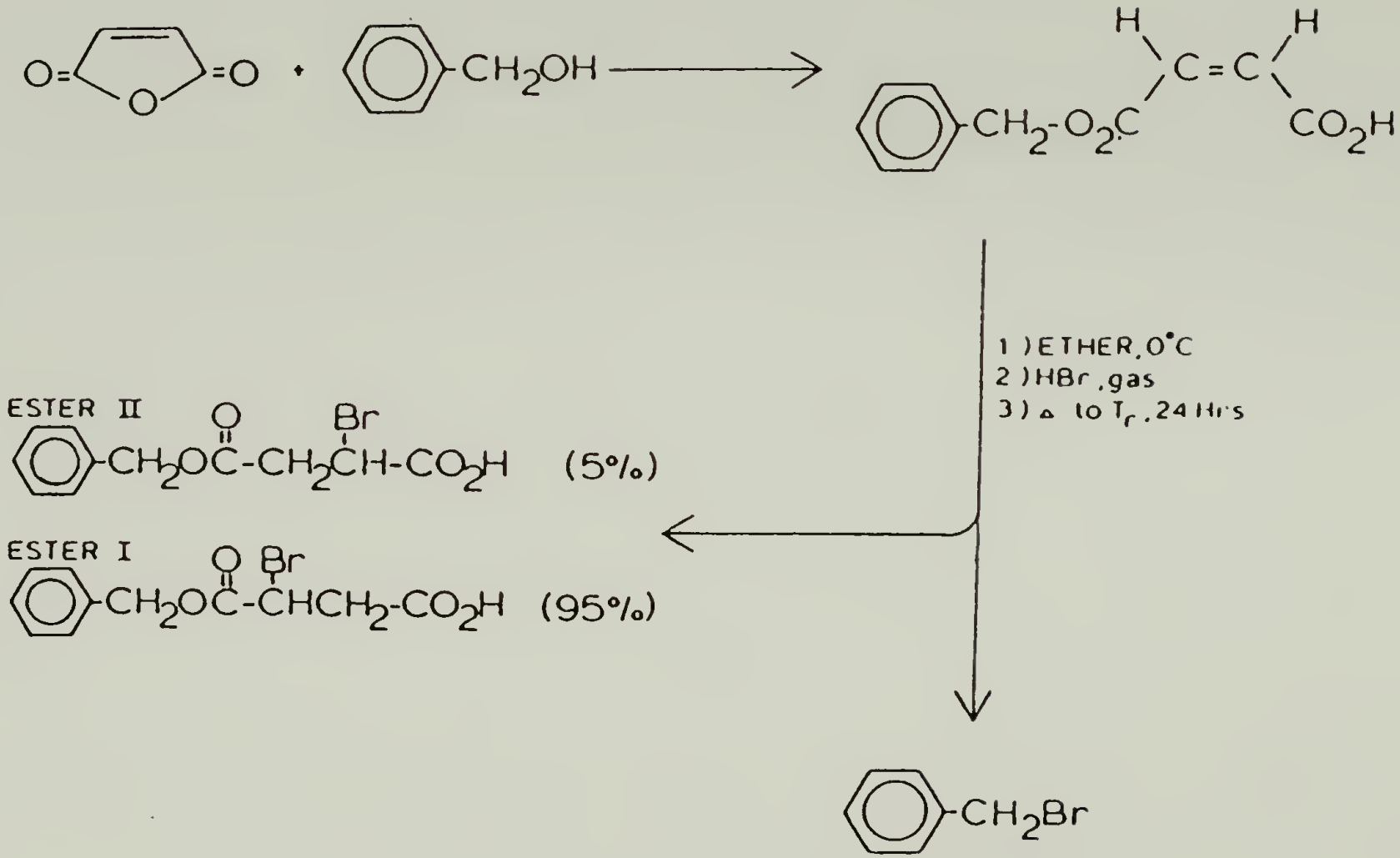


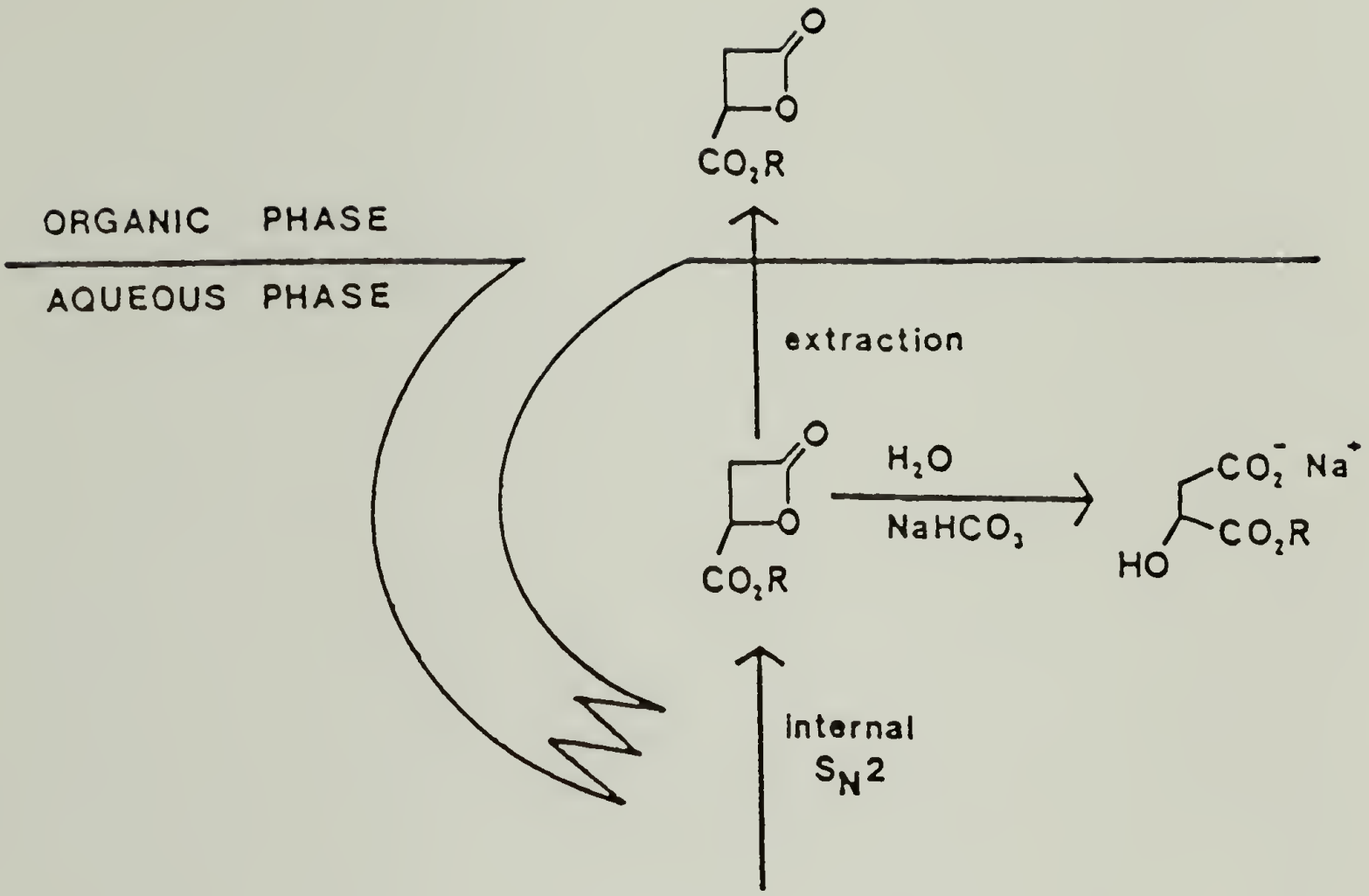
Figure 2.2 Alternative synthesis of benzyl bromosccinate(s).

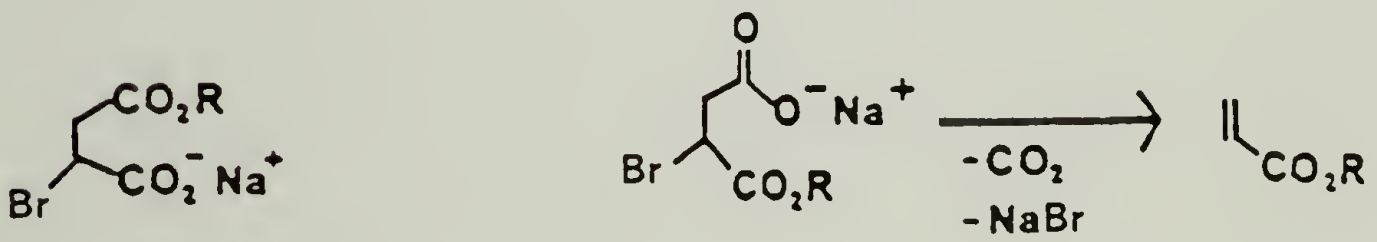
The preparation of benzyl malolactonate was carried out directly from the mixture of the two benzyl bromosuccinates, of which only ester (I) is capable of ß-lactone formation. Attempts were made at separating the two esters by either fractional distillation, recrystallization, column chromatography or HPLC, but all were without success.[5]

A two-phase system was used for the lactonization reaction, and a dilute solution was used to promote the intramolecular reaction for lactone formation as opposed to intermolecular reactions. Benzene was found to be a better solvent than either dichloromethane or diethyl ether for producing the lactone in a high yield.[5] No catalyst was used in this reaction.

The formation of benzyl malolactonate in the organic phase was readily monitored by IR spectroscopy because the lactone carbonyl group strongly absorbs at 1850 cm^{-1} (IR #3). As shown in Figure 2.3, under this condition the benzyl ester (I) will undergo an internal S_N2 reaction, and the ß-lactone, which is formed, is continuously extracted into the organic layer before it reacts further. The reaction temperature was kept under 45°C so that side reactions, such as decarboxylation of ester (I) and/or the hydrolysis of the ß-lactone, would not compete with lactonization. Isolating the lactone from the benzene phase every two hours improved the yield from 70 to 90%.

Benzyl malolactonate was obtained as a water-white, slightly viscous, oily material. It was necessary to further purify the lactone in order for the polymerization to yield high molecular





R = CH_2Ph

Figure 2.3 Lactonization of racemic benzyl bromosccinate (I) to form [R,S]-BML.

weight PBL, but decomposition and thermal-polymerization which readily occurred during monomer distillation made the initial purification difficult. It was found that the success of the distillation was strongly dependent on both the initial monomer purity and the temperature control in the procedure. Two improvements were made in this work which greatly increased the yield from 50 to 85%. Firstly, an extraction was performed on the crude lactone to remove some impurities prior to distillation, and secondly, the distillation was completed as soon as possible under high vacuum (10^{-5} mm) at a temperature lower than 95°C because either longer time or higher temperature resulted in either decomposition or thermal polymerization. Only an extremely short path distillation column of 2 to 3 cm in length (see Figure 2.4) and small quantities of lactone could be used. Under these conditions it was possible to distill the crude lactone directly without prepurification by preparatory HPLC. After two distillations, no impurities were detected by analytical HPLC[5] and by ^{1}H NMR.

2.1.2 Catalyst Preparations

The addition of water or alcohol to the coordination catalysts such as R_3Al, R_2AlCl and R_2Zn has been found to increase the rate of polymerization of epoxides, acetaldehyde and lactones, and also to increase the molecular weight of the polymer formed,[11,13-14] but the nature of the actual active site is unclear yet. Such co-catalysts most likely modify the active site of the catalyst species, as is believed to be the case for the reaction product of

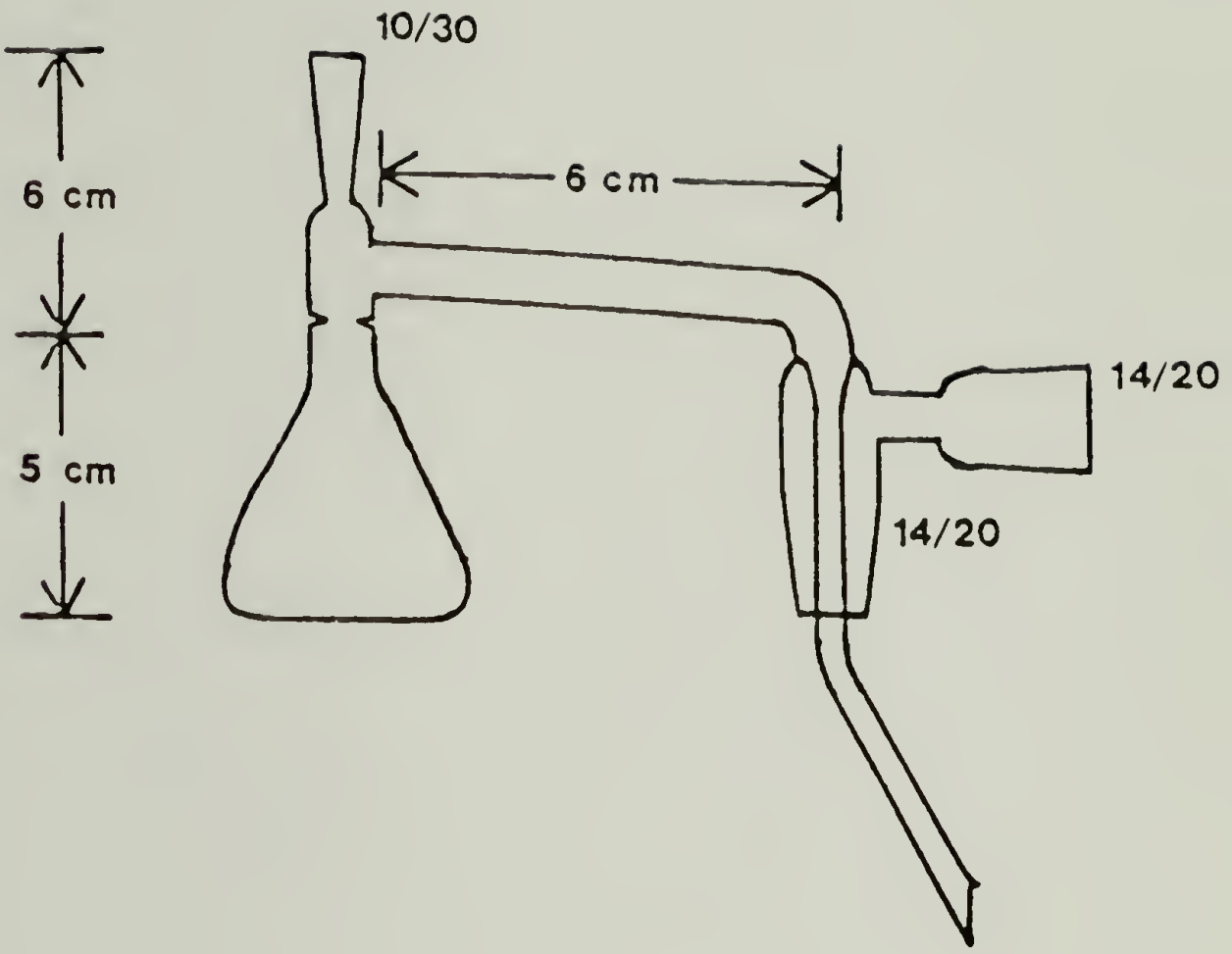


Figure 2.4 Short path distillation column.

water and aluminum.[10]

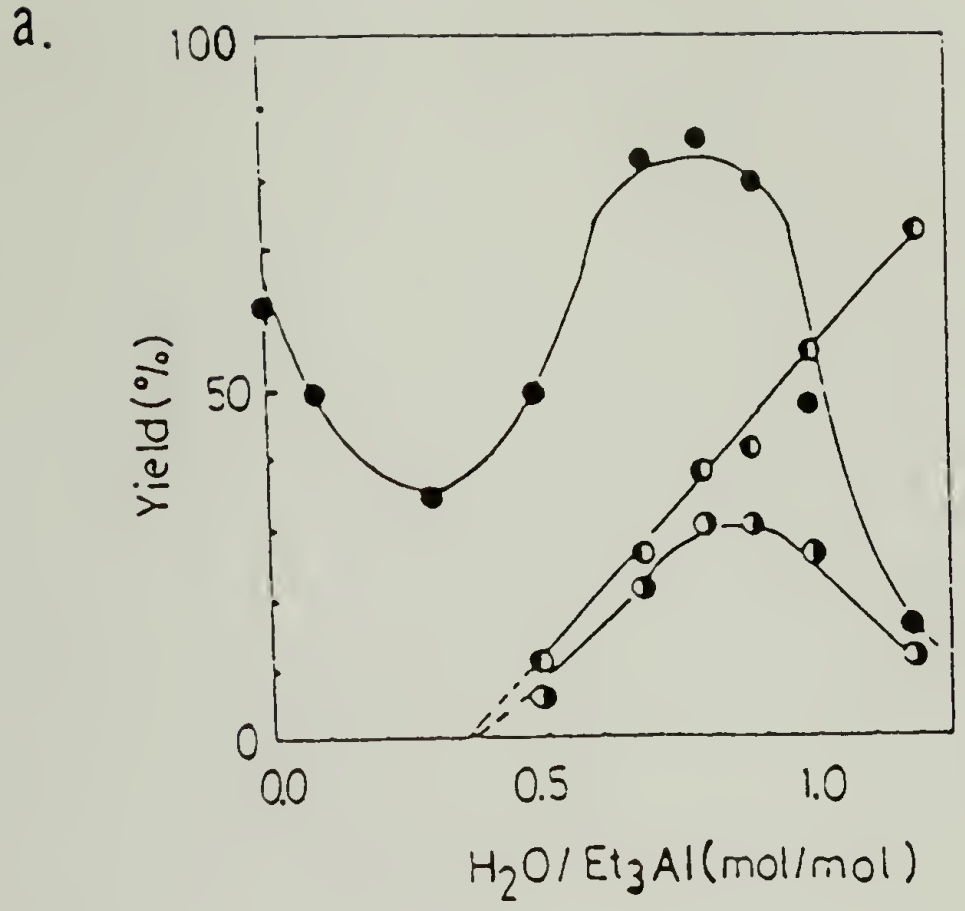
2.1.2.1 "*In-situ*" Catalyst of Et_3Al/H_2O

Molar ratios of H_2O to Et_3Al of 1.45/1.0 and 1.0/1.0 were selected in this study for the preparation of the "*In-situ*" Catalyst. The activities of this catalyst with respect to different H_2O/Et_3A ratios for the polymerization of acetaldehyde, epoxide, and ß-butyrolactone (ß-BL) have been investigated by Tani and coworkers.[11,13-14] The highest catalytic activity for the stereospecific polymerization of ß-BL was obtained at the molar ratio of 1:1, as shown in Figure 2.5-a.[11] In contrast, it was reported by Marchessault and coworkers that the catalyst with a molar ratio of 1.45:1.0 usually produced the highest total yield of poly-ß-butyrolactone, PBL, shown in Figure 2.5-b.[12]

In the "*In-situ*" catalyst preparation, water was added slowly to the Et_3Al solution at -78°C to prevent an explosion or too vigorous reaction. A microsyringe was used for the water injection in order to control precisely the reaction ratio of H_2O and Et_3Al.

2.1.2.2 Ethylaluminoxane, EAO

There are several factors that effect the activity of Et_3Al/H_2O catalyst, including: (1) ratio of Et_3Al/H_2O; (2) method used in the preparation of the catalyst; (3) solvent, (4) thermal and vacuum treatment; (5) reaction time during the catalyst preparation and (6) additives. It is difficult, therefore, to obtain good reproducibility for preparing the *"In-situ"* catalyst, but the



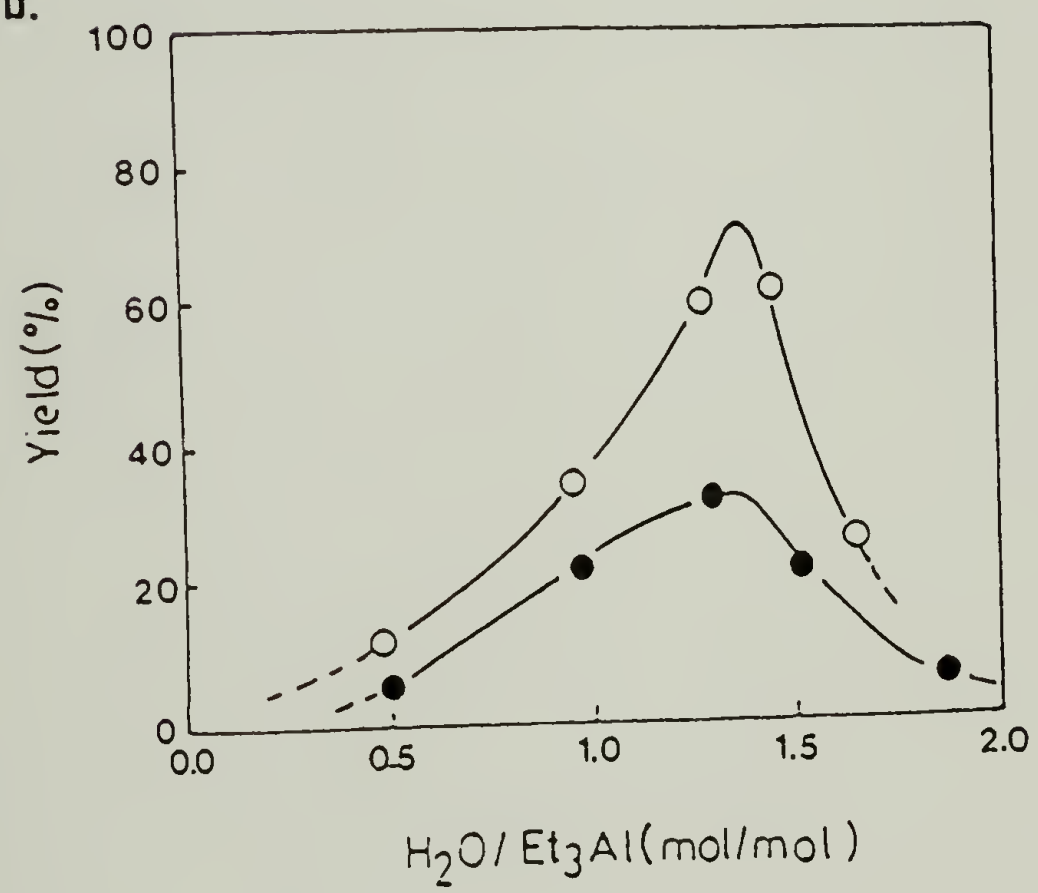


Figure 2.5 Effect of the ratio of $H_2O/AlEt_3$ on yield of the polymerization of racemic β-BL.
(a) Polymerization conditions: monomer, 2.0 mL; solvent, toluene 2.0 mL; catalyst, 2.0 mol% of monomer; time, 7 days; temperature 60°C. ● total yield; ◑ crystalline polymer yield; ◐ index of stereospecificity.[11]
(b)[12] Polymerization were performed in 4.0 mol% catalyst, at 60°C for 7 days. ○ bulk polymerization; ● 5 mL $CHCl_3$ per mL monomer.

oligomeric catalyst obtained from the reaction of Et_3Al and water, termed ethylaluminoxane, EAO, was reported to have a much better reproducibility than the *"In-situ"* catalyst for the stereoregular polymerization of ß-propiolactone.[11,13-15] The EAO catalyst was prepared by the reaction of Et_3Al and H_2O in a 1:1 ratio, followed by a high vacuum treatment to produce an oligomer, which is formulated as $-[-Al(Et)-O-]-_n$, with both cyclic (A) and linear (B) components, as shown in Figure 2.6-a.[15,19] The degree of polymerization of the catalyst can vary from 10 to 20, depending on the conditions under which it is prepared (Table 2.1).[11,15,19]

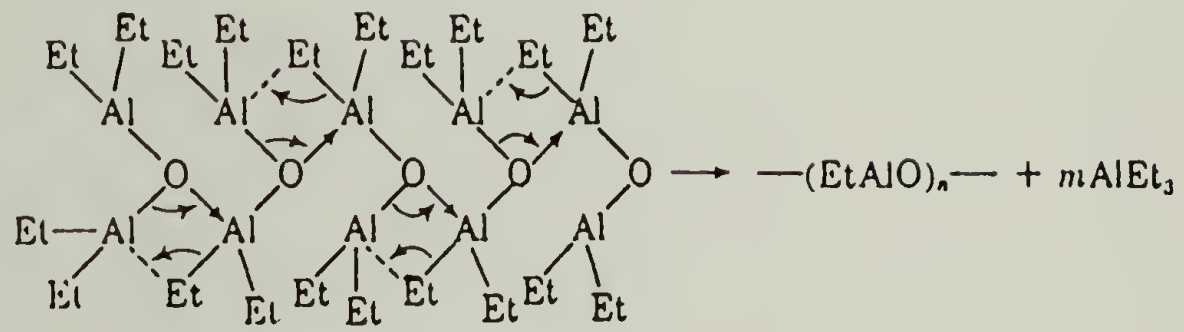
The most successful method used in the present study for obtaining the stereoregular EAO catalyst involved a removal of the unreacted $AlEt_3$ (I) and $Et_2AlOAlEt_2$ (II), which are formed as undesireable reaction products, by distillation under high vacuum. Decalin was used in the distillation to help to remove I and II because of the similarity of their boiling temperatures. Both I and II as well as the hydroxylated organoaluminum compounds, which are formed in the Et_3Al/H_2O reaction, have been reported to have severely adverse effects on the stereoregular polymerization of lactones.[13,17] At the end of distillation the bath temperature was kept at 180-190°C for half an hour to allow further disproportionation, so a higher oligomer was formed, as shown in Figure 2.6-b.

The isolated EAO catalyst obtained after solvent distillation was a white amorphous powder which was soluble in toluene and hexane. The amorphous nature of the product was confirmed by X-

a.

$$n\,Et_3Al + n\,H_2O \xrightarrow[PHCH_3]{-70^{\circ}C} Et_2Al(OAlEt)_{n-1}OH + (2n-1)\,EtH$$

b.



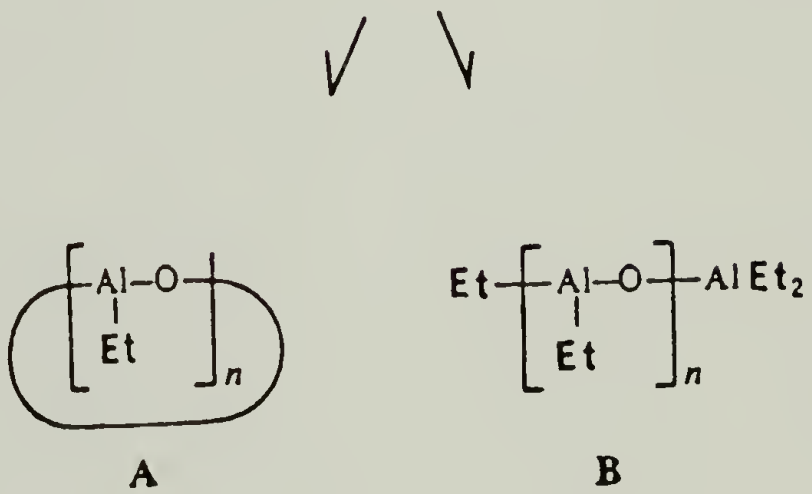


Figure 2.6 Preparation of ethylaluminoxane (EAO).
(a) Equimolecular reaction of Et_3Al and H_2O;
(b) Disproportionation at 10^{-4} mm and 180°C.

Table 2.1 The degree of polymerization of oligomeric alkylaluminoxane, $-[AlRO]_n-$

Auther	$-[AlRO]_n-$	degree N [a]
Tani *et al.*[11]	EAO	10
Kaminsky[15]	MAO	6-20
Giannetti[19]	MAO	23-28
Benvenuti[b]	EAO	11
This work[c]	EAO	15-17

a The number of N were determined by cryoscopy in benzene.

b The EAO was prepared under vacuum without high temperature treatment.

c The EAO synthesized in this work was treated under high vacuum and high temperature 180-190°C.

ray diffraction.[19] The aluminum content of the oligomer varied within the range of 33.7 to 34.5%, and the Et:Al ratio was exactly 1:1. The degree of oligomerization, as determined by cryoscopy in dry benzene, varied from 15 to 17. The ^1H NMR spectrum (see ^1H NMR #8) displayed two broad bands at 0.35 and 1.14 ppm, which are attributable to the methylene and methyl protons of the $[Al(CH_2CH_3)O]_n$ oligomer. The observed broadening of the resonance lines in the spectrum may be attributed either to the presence of oligomers having different structures (cyclic or linear) or to the polymeric nature and association tendency of the ethylaluminoxane. The EAO synthesized in this study was stable even after storage in an argon atmosphere for about one year.

The degree of oligomerization of the EAO catalyst was not very reproducible if water was used directly in the catalyst synthesis because the reaction between $AlEt_3$ and water was difficult to control. This shortcoming was avoided by using $Al_2(SO_4)_3 \cdot 6H_2O$ as a water source, as reported by Kaminsky and coworkers.[19,20] EAO can also be obtained from the conversion of $Et_2AlOAlEt_2$ by a disproportionation reaction which eliminates Et_3Al under high vacuum,[11,17-18] but this reaction was not used in the present study.

2.1.2.3 Diethylzinc-Water Catalyst, Et_2Zn/H_2O

This catalyst, which is also believed to have an oligomeric structure that can be represented as $Et(ZnO)_nZnEt$, was derived from the reaction of Et_2Zn and H_2O in a 1:0.6 molar ratio at

-78°C.[13,14,26-28] Dry 1,4-dioxane which was used as solvent for the reaction helped in the removal of unreacted Et_2Zn through distillation because of the similarity of their boiling temperatures. The reaction was initially carried out at -78°C because of the exothermic nature of the reaction and the evolution of ethane: the mixture was then slowly warmed to room temperature. A yellow or ceramic colored powder, which was believed to be $Et(ZnO)_2ZnEt$, was obtained after vacuum treatment.[13-14]

2.1.2.4 (5,10,15,20-Tetraphenylporphinato)aluminum Chloride, TPPAlCl

Equimolar amounts of tetraphenylporphinato dihydride ($TPPH_2$) and Et_2AlCl were reacted to form this catalyst, TPPAlCl, with the structure shown in Figure 2.7. Rapid evolution of about 2 equivalents of ethane with respect to $TPPH_2$ was observed. A 20 mol% excess of Et_2AlCl was used to ensure that no unreacted $TPPH_2$ remained after the reaction because the active hydrogen atoms in $TPPH_2$ are even more reactive with monomers than is Et_2AlCl. The excess Et_2AlCl was readily removed by vacuum distillation. The TPPAlCl catalyst must be prepared under an argon atmosphere excluding any trace of water, otherwise the living character of the catalyst will be effected.[20-23]

2.1.2.5 Catalyst Solutions

All of the catalyst solutions were prepared by dissolving the above catalysts in dry toluene, which is also a good solvent for the monomers investigated in this study. Hence, all polymerization

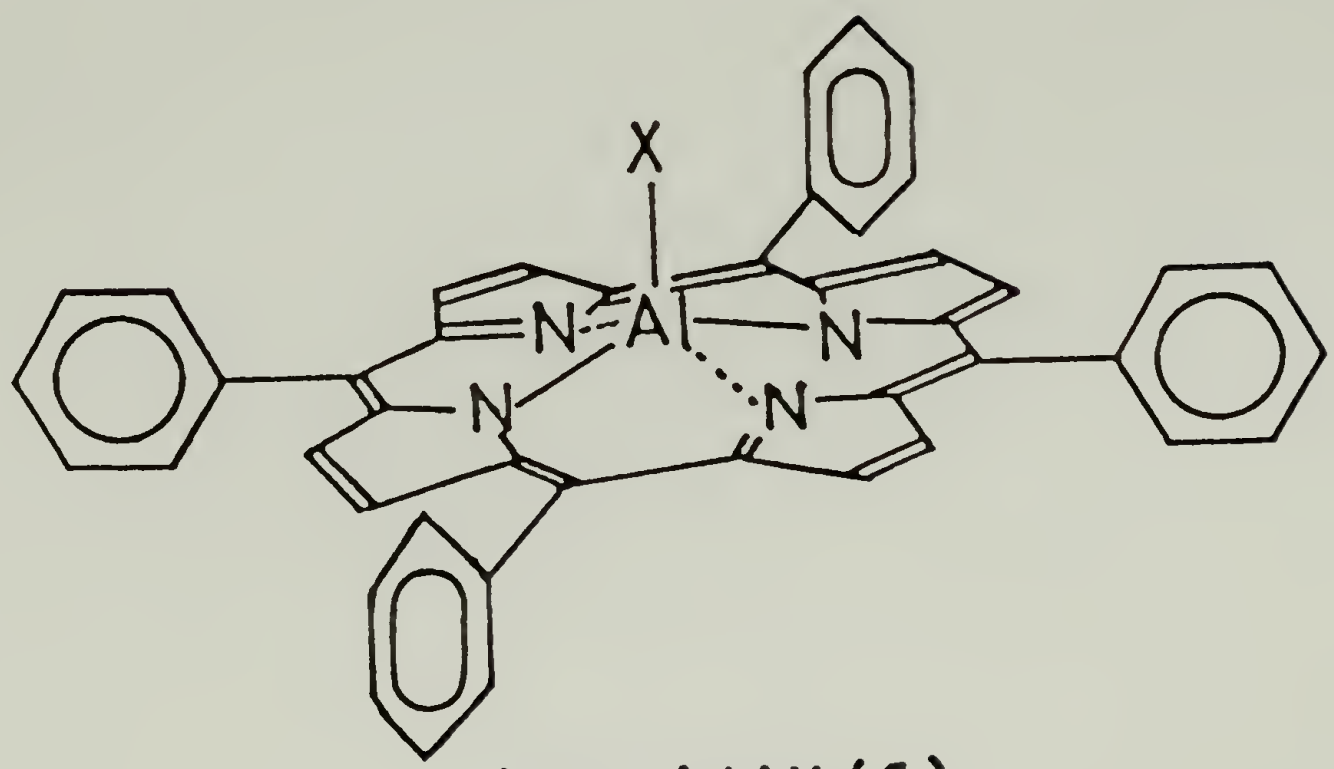


Figure 2.7 Structure of (5,10,15,20-tetraphenylporphinato)aluminum chloride (TPPAlCl).

reactions were initially homogeneous. Toluene was found to be a better solvent than either diethyl ether,[20] hexane or chloroform[24] for both temperature control and obtaining high yields.

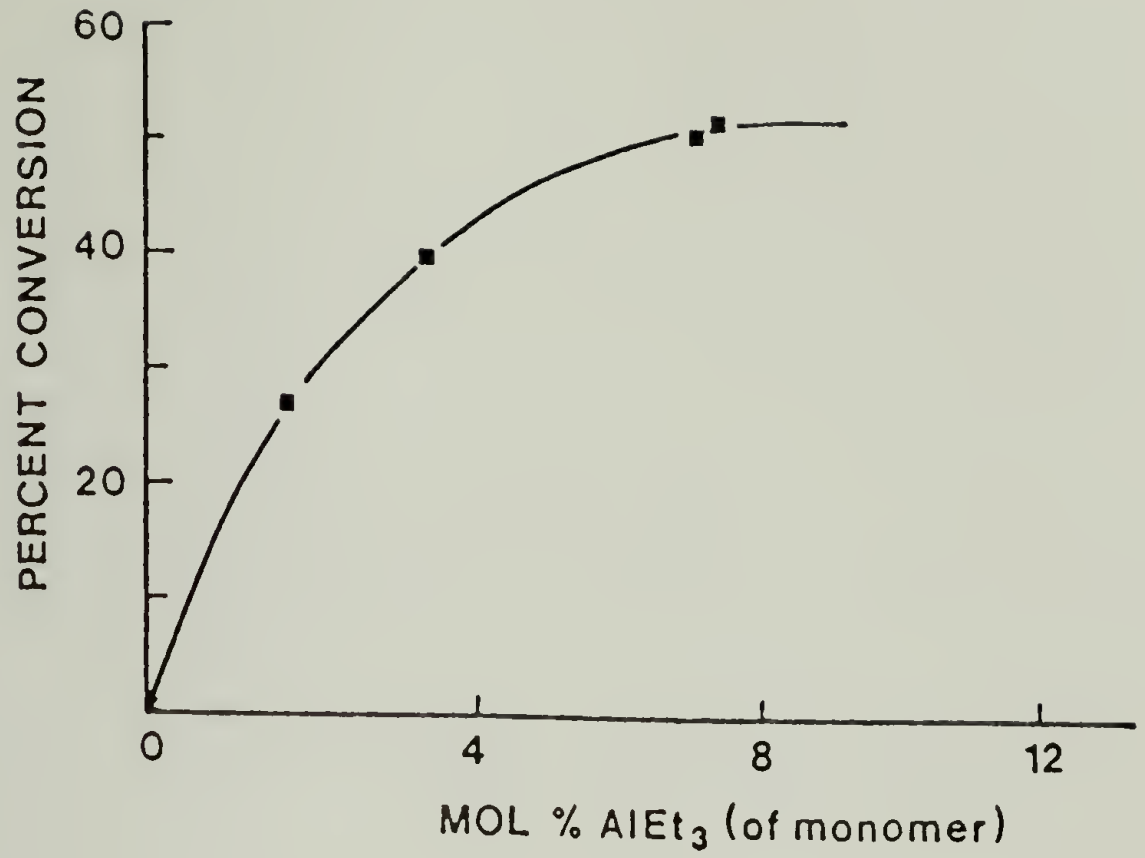
2.1.3 Polymerizations of Butyrolactone and Benzyl Malolactone

2.1.3.1 Optimization of the Polymerization Reactions

In the polymerization reactions of racemic ß-substituted-ß-propiolactone monomers, the useful variables include temperature, time, and amount of catalyst (as shown in Figure 2.8-a), all of which can influence the yield and the stereoregularity of the polyesters formed. An optimum temperature of 60°C was suggested by Tani and coworkers,[13-14] who showed that for the polymerization of ß-BL the yield of PBL increased with increasing temperature up to 100°C, but the yield of crystalline polymer decreased significantly above 60°C. Therefore, in the present study, all polymerizations were performed at the latter temperature. The time dependence for PBL formation, shown in Figure 2.8-b, exhibited a linear increase of yield in the preparations of both the stereoregular (acetone-insoluble) and the non-stereoregular (acetone-soluble) PBL using the Et_3Al-H_2O (1:1) catalyst. However, some polymer degradation reactions may occur at longer reaction times.[13]

For achieving both stereoregularity and high molecular weight products, the polymerization times of ß-BL and ß-BML were 7 days and 14 days, at 60°C, for the "*In-situ*" catalyst and the alkyl

a.



b.

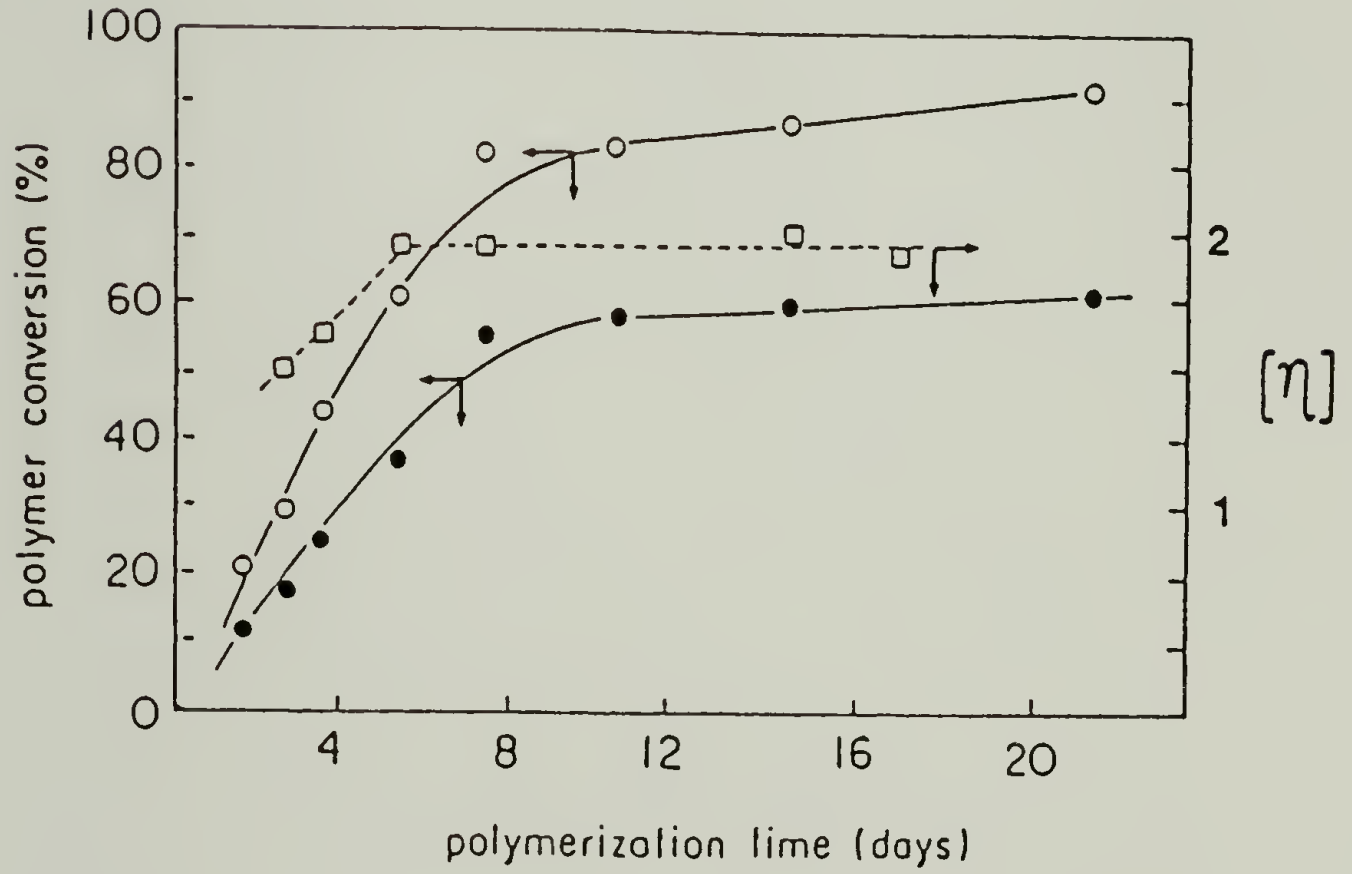


Figure 2.8 Optimum of the polymerization of β-BL.
(a) Effect of amount of $H_2O/AlEt_3$ (1.3:1) catalyst on percent conversion of poly([R,S]-HB) (bulk polymerization).
(b) Effect of polymerization time on percent conversion of poly([R,S]-HB). ○ total polymer yield, ● stereoregular polymer yield and □ [η] of the stereoregular polymer in $CHCl_3$ at 30°C.

aluminoxanes catalysts, respectively. The effect of the amount of catalyst on the conversion of racemic ß-BL to PBL is shown in Figure 2.8-a. No appreciable increase in polymer yield was observed at levels higher than 0.08 molar equivalents of catalyst to monomer.

2.1.3.2 Homopolymerization of ß-BL

(i) Aluminum-Water Based Catalysts The results of the polymerization reactions with the "*In-situ*" and EAO catalysts are summarized in Table 2.2 (a & b). The crude yields obtained ranged from 30 to 50 wt%. For the crude polymer products synthesized from [R,S]-ß-BL, fractionation into high and low crystalline fractions was an important step in obtaining information obout this stereoregular polymerization. The differences in solubility of these polymers were used for the fractionation, as shown in Figure 2.9.

Treatment of the crude, yellow polymers with acetylacetone (AcAc)[14] was used for removal of the colored impurities and aluminum in the products. After the AcAc treatment, a white highly crystalline polymer was obtained having an increased molecular weight and a greatly decreased aluminum content. For example, Polymer 3 in Table 2.2, prior to AcAc treatment, had a molecular weight three times lower than that of the purified polymers. The unpurified polymer had an enthalpy of fusion, ΔH_m, of 1.3 cal/g, as compared to 12.3 cal/g for the sample after the AcAC treatment. The aluminum contents of these polymers, as

Table 2.2 The polymerization of [R,S]-BL using the aluminum-water catalysts

(a) The homopolymerization of [R,S]-BL using the catalysts derived from the reaction of R_3Al and H_2O.

Sample	Catalyst[b]	polymztn time (days)	molar ratio H_2O/AlR_3[a]	mol % Al/Monomer	yield crude (%)	yield after AcAc treatment (%)	yield of acetone insol fractn % from monomer	yield of acetone insol fractn % from AcAc prod
1	In situ	7	1.45	6.0	55	17	11	(65)
2	In situ	7	1.45	6.0	31	13	10	(77)
3	In situ	7	1.0	4.0	45	6	4	(67)
4	MAO	14	1.0	4.0	22	20	16	(80)
5	EAO	14	1.0	4.0	40	20	15	(75)
6	EAO	14	1.0	0.5	30	20	12	(60)
7	EAO	60	1.0	1.4	52	42	26	(62)
8	IBAO	7	1.0	4.0	40	20	15	(75)

a samples 1-3 and 5-7 R=Et, sample 4 R=Me, sample 8 R=i-Bu

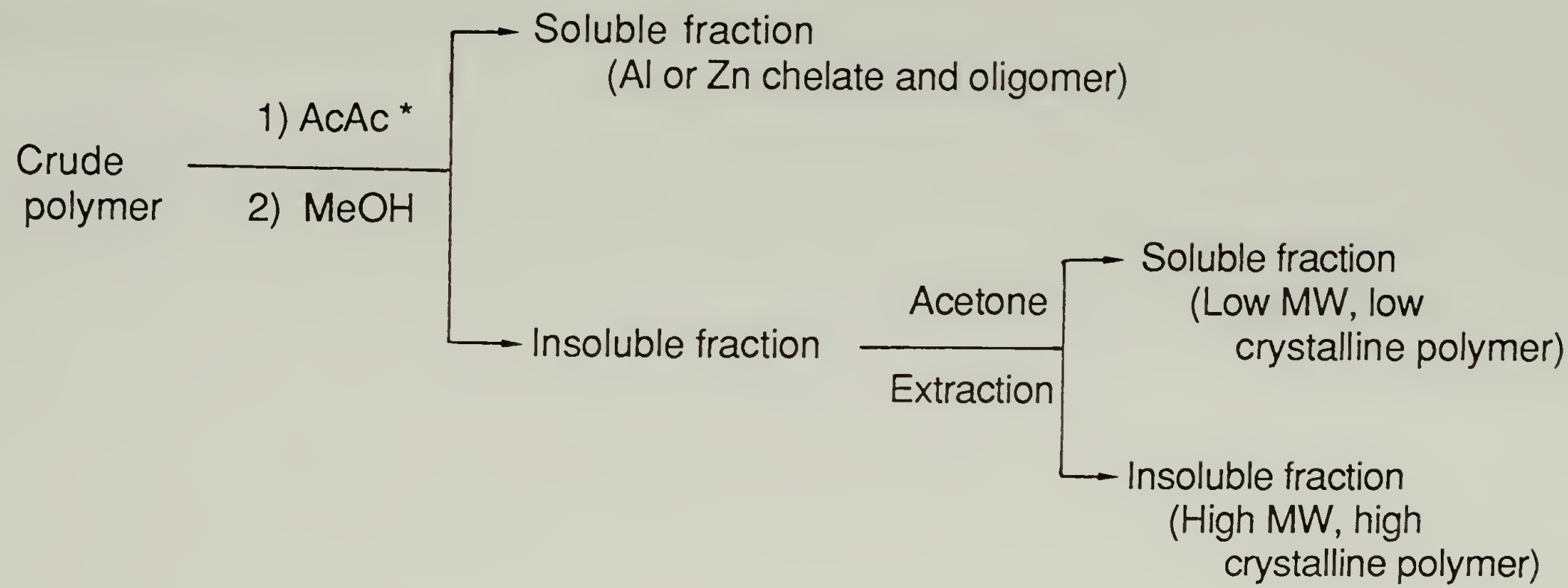
b The in situ catalyst was prepared directly in the polymerization ampule, EAO is ethylalumoxane $([AlEt\text{-}O\text{-}]_n)$, MAO is methylalumoxane $([AlMe\text{-}O\text{-}]_n)$, IBAO is isobutylalumoxane $([AlBu\text{-}O\text{-}]_n)$.

c AcAc is Acetylacetone

(b) Characterization of the product fractions in Table 2.2 (a).

Sample	Molecular Weight Determination (GPC)[a]						ΔHm,[d] cal/g		Peak melting temp, °C	
	AcAc[b] treated prod[c]		acetone-sol fractn		acetone-insol fractn		AcAc treated prod	acetone insol fractn	AcAc treated prod	acetone insol fractn
	$\frac{\overline{M}_w}{\overline{M}_n}$	$(\overline{M}_w/\overline{M}_n)$	$\frac{\overline{M}_w}{\overline{M}_n}$	$(\overline{M}_w/\overline{M}_n)$	$\frac{\overline{M}_w}{\overline{M}_n}$	$(\overline{M}_w/\overline{M}_n)$				
1	$\frac{380,000}{36,000}$	(11)	$\frac{80,000}{22,000}$	(3.6)	$\frac{290,000}{39,000}$	(7.4)	9.8	16.0	162	166
2	$\frac{730,000}{43,000}$	(17)	$\frac{30,000}{9,500}$	(3.2)	$\frac{440,000}{80,000}$	(5.5)	9.0	14.0	159	165
3	$\frac{410,000}{32,000}$	(13)	$\frac{160,000}{18,000}$	(8.9)	$\frac{300,000}{47,000}$	(6.4)	12.3	17.6	163	165
4	$\frac{310,000}{35,000}$	(8.9)	$\frac{99,000}{22,000}$	(4.5)	$\frac{620,000}{100,000}$	(6.2)	12.9	15.9	160	164
5	$\frac{632,000}{77,000}$	(8.2)	$\frac{92,000}{20,000}$	(4.6)	$\frac{970,000}{100,000}$	(9.7)	9.7	16.7	161	163
6	$\frac{1,000,000}{63,000}$	(15)	$\frac{600,000}{110,000}$	(5.5)	$\frac{1,500,000}{200,000}$	(7.5)	12.0	18.5	161	169
7	$\frac{640,000}{85,000}$	(8.0)	$\frac{200,000}{43,000}$	(4.7)	$\frac{840,000}{130,000}$	(6.6)	11.0	17.5	163	167
8	$\frac{571,000}{52,000}$	(11)	$\frac{121,000}{40,000}$	(3.0)	$\frac{1,000,000}{139,000}$	(7.0)	11.0	14.8	161	163

[a] Eluted with $CDCl_3$ at 25°C; the molecular weight averages were calculated on the based of polystyrene standards.
b AcAc is acetylacetone.
c Partially fractionated product which remained after AcAc treated.
d Determined by DSC during the first heating scan.



* AcAc is acetylacetone.

Figure 2.9 Fractionation of polymers

shown in Table 2.3, were 2.2% and 0.05% before and after AcAc treatment, respectively.

Both the "*In-situ*" and the EAO catalysts produced the acetone-insoluble fractions of PBL having high degrees of stereoregularity and high molecular weight. DSC spectra of the acetone-insoluble and -soluble fractions of polymer 4 are shown in Figure 2.10-a and b. These polymers had melting temperatures of 163° and 143°C, for the above two fractions, respectively. The ΔH_m values of the acetone-insoluble fractions, listed in Table 2.2-b, ranged from 14.0 to 18.5 cal/g, while the value of naturally occurring P([R]-HB), which is completely isotactic in structure, is 22 cal/g.[26,27] These results indicate that the acetone-insoluble fractions have degrees of crystallinity of approximately 80% of that of the natural PHB. The increase in the peak melting temperature by approximately 30°C in combination with the higher values of enthalpy of fusion for the acetone-insoluble fractions, also indicates that these polymers have much higher degrees of stereoregularity than that of the soluble-fractions.

By using ^{13}C NMR analysis for a measurement of polymer tacticity, it is possible to determine and compare the stereoregularity of PBL obtained from racemic BL with the different catalysts. The ^{13}C NMR spectrum of PBL synthesized with the $ZnEt_2/H_2O$ catalyst has a carbonyl carbon peak, which is sensitive to tacticity,[28] as shown in Figure 2.11. The diad sequences of this amorphous PBL, in the carbonyl carbon region, can be clearly seen from the two peaks presented in Figure 2.12-c. The

Table 2.3 Metal (Al or Zn) contents in the catalysts and polymer fractions.

Sample	Polymer	Fraction	Catalyst[a]	Al or Zn wt.%
MAO	$[AlMe\text{-}O\text{-}]_n$			41.1 (46.6)[b]
EAO	$[AlEt\text{-}O\text{-}]_n$			32.7 (37.5)
3	P([R,S]-HB)	crude	$AlEt_3/H_2O$	2.2
3	P([R,S]-HB)	AcAc[c] treated	$AlEt_3/H_2O$	≤0.05
3	P([R,S]-HB)	acet-insol fractn	$AlEt_3/H_2O$	≤0.01
10	P([R,S]-HB)	crude	$ZnEt_2/H_2O$	4.10
12	P([R,S]-HB)	crude	TPPAlCl	≤0.30
24	P(HB-BM) (50:50)	crude	EAO	1.7
24	P(HB-BM) (50:50)	AcAc treated	EAO	≤0.01
24	P(HB-BM) (50:50)	acet-sol fractn	EAO	≤0.10
36	P([S]-HB)	AcAc treated	$ZnEt_2/H_2O$	≤0.07

a EAO is ethylalumoxane ([AlEt-O-]n), MAO is methylalumoxane ([AlMe-O-]n).

b The value inside bracket is theoretic metal content calculated from the repeating unit.

c AcAc is acetylacetone.

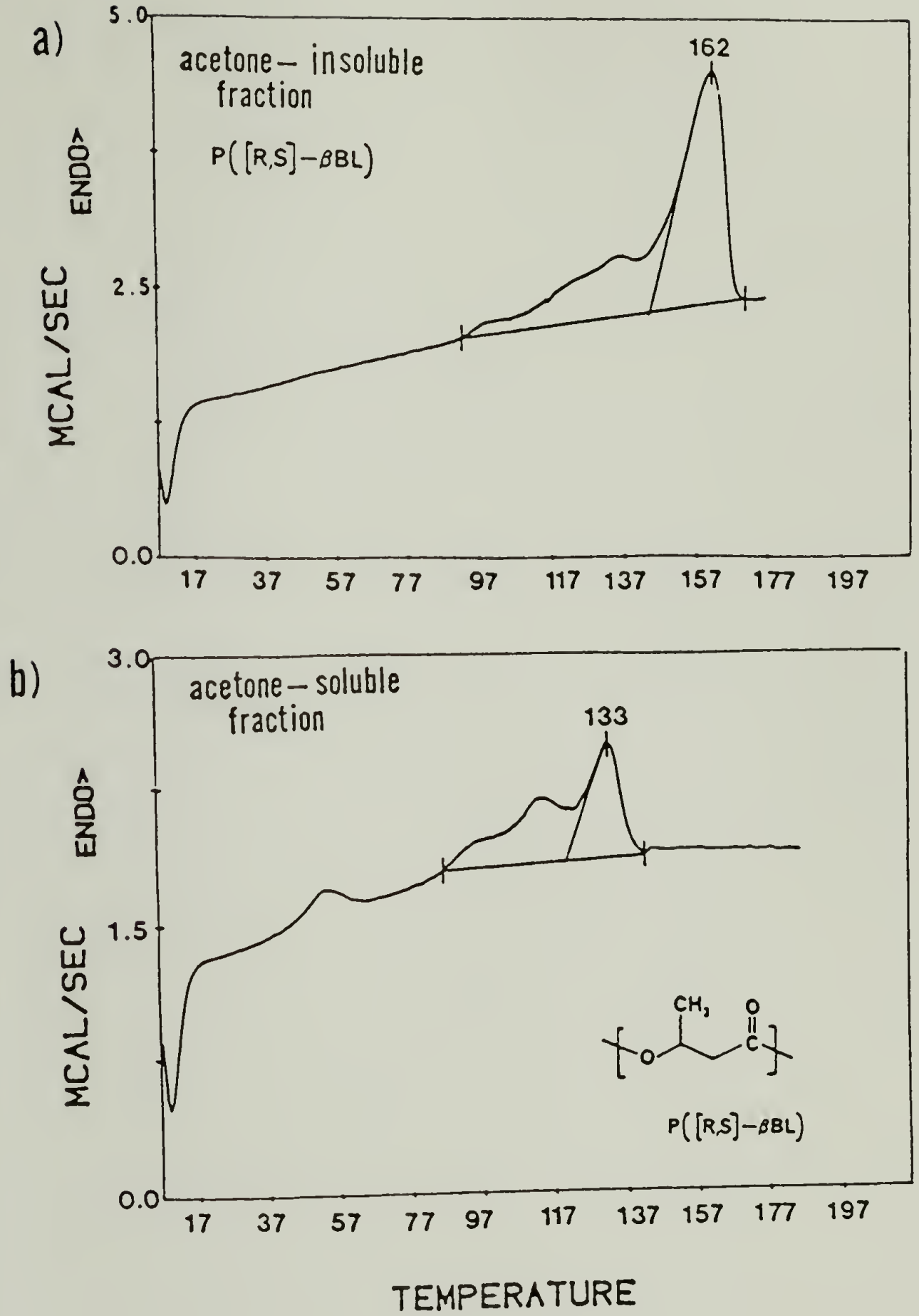
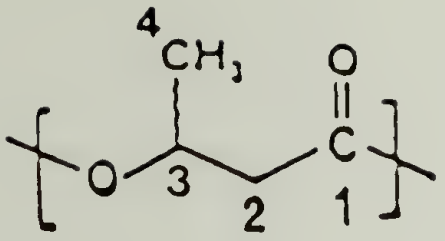


Figure 2.10 DSC thermograms of P([R,S]-HB) synthesized using the EAO catalyst.



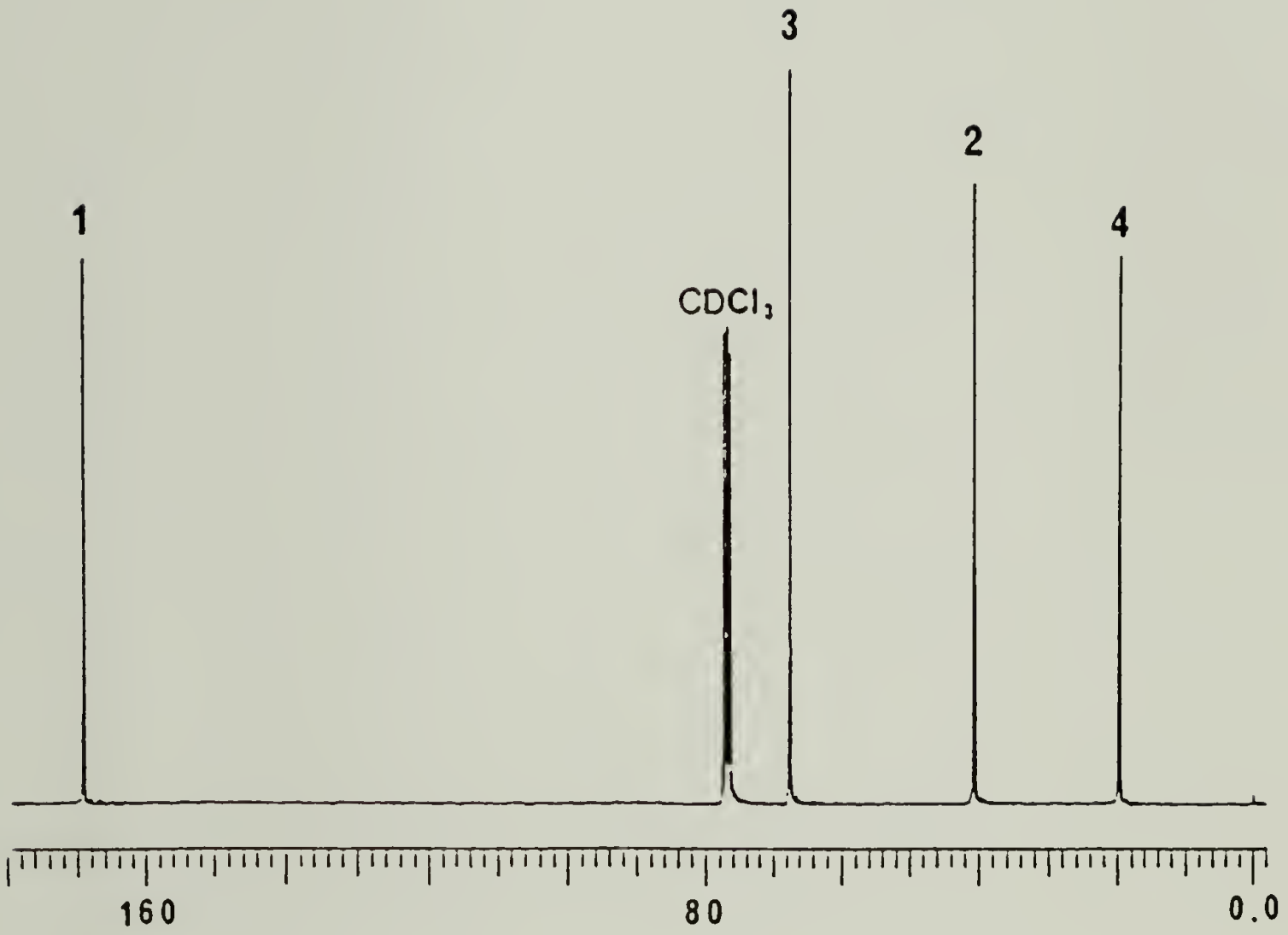
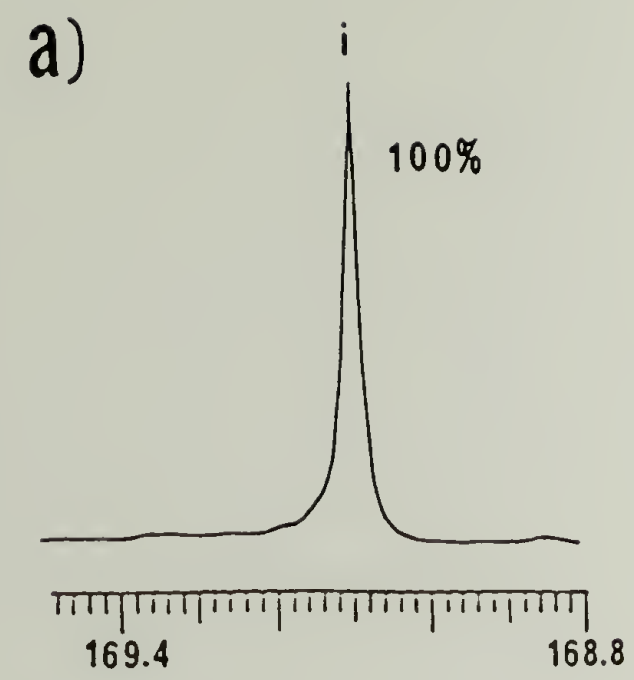
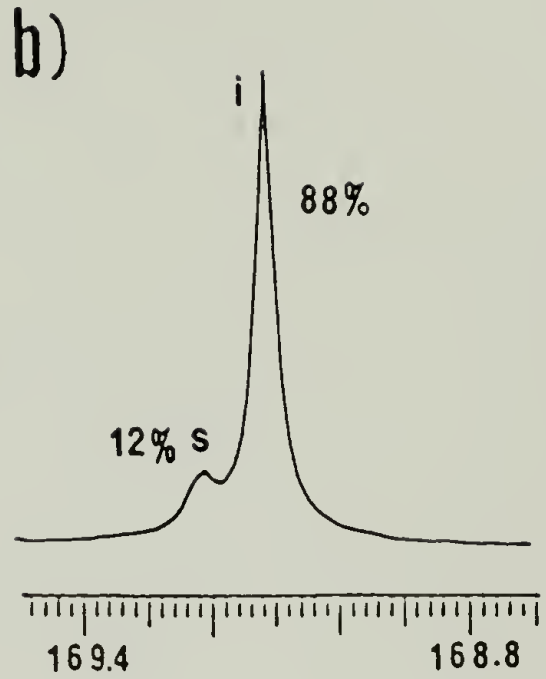
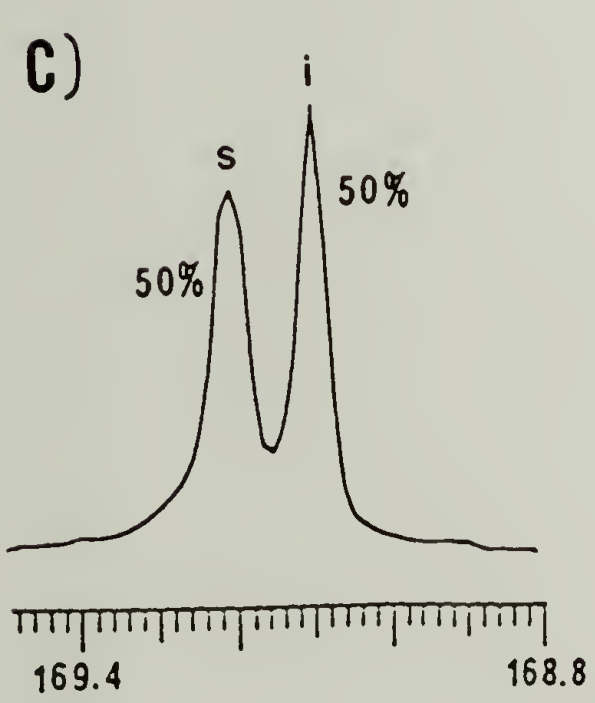


Figure 2.11 ^{13}C NMR spectrum of P([R,S]-HB) synthesized using the $ZnEt_2/H_2O$ catalyst.







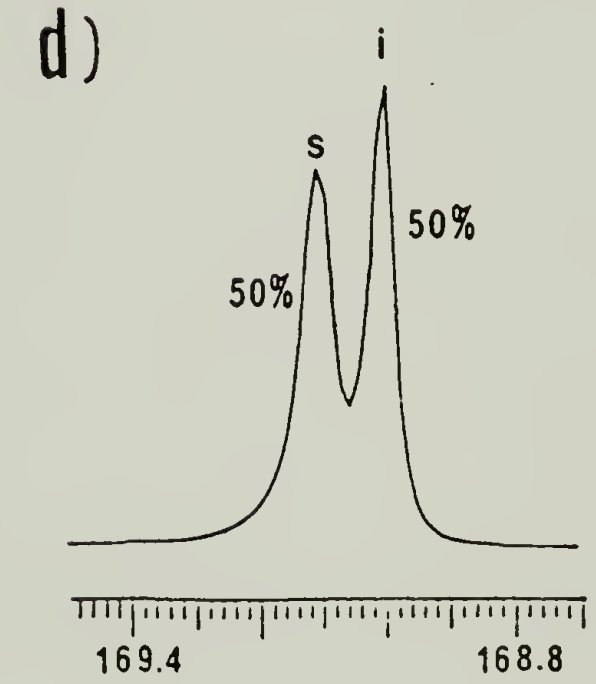


Figure 2.12 Expansions of carbonyl carbon of the PHB synthesized using the different catalysts. (a) Natural origin P([R]-HB); (b, c and d) P([R,S]-HB) synthesized using the catalysts EAO, $ZnEt_2/H_2O$ and TPPAlCl, respectively.

upfield and downfield peaks correspond to isotactic (i) (R-R and S-S) and syndiotactic (s) (R-S and S-R) stereochemical sequences, respectively.[28] The positive identification of the upfield signal was obtained by mixing the racemic polymer, P([R,S]-BL) with natural origin polymer, P([R]-HB).[29]

The expansion of the carbonyl carbon region of PBL 5, which was synthesized with the EAO catalyst, is shown in Figure 2.12-b. By integrating the areas of the (i) and (s) signals, a value of 88% isotactic diads was obtained for this polymer. A similar result of 85% (i) diads was observed for PBL 1 obtained from the *"In-situ"* catalyst. The higher fraction of isotactic diads in these samples indicates that the polymers contain longer sequences with the same stereochemical configuration; that is, isotactic blocks. The acetone-soluble fractions of Polymers 1-4 had approximately 60% (i) diads, which is consistent with the lower enthalpy of fusion (ΔH_m= 6.6 cal/g) and lower melting temperature observed in the DSC spectra for these fractions, as shown in Figure 2.10-b.

Fourier transfer infrared spectroscopy (FTIR) can also be used to determine the polymer crystallinity as an indication of the degrees of stereoregularity of the polymer samples. Figure 2.13 shows the FTIR spectrum of PBL 5, which was obtained with the EAO catalyst. The expanded region of the spectrum for this sample, as shown in Figure 2.14-a, indicated a similar crystallinity to that of natural origin PHB. The specific peak for this determination is the one at 1280 cm^{-1}, a strong absorption for the methyl group, which is an indication of the sample's crystallinity. A different

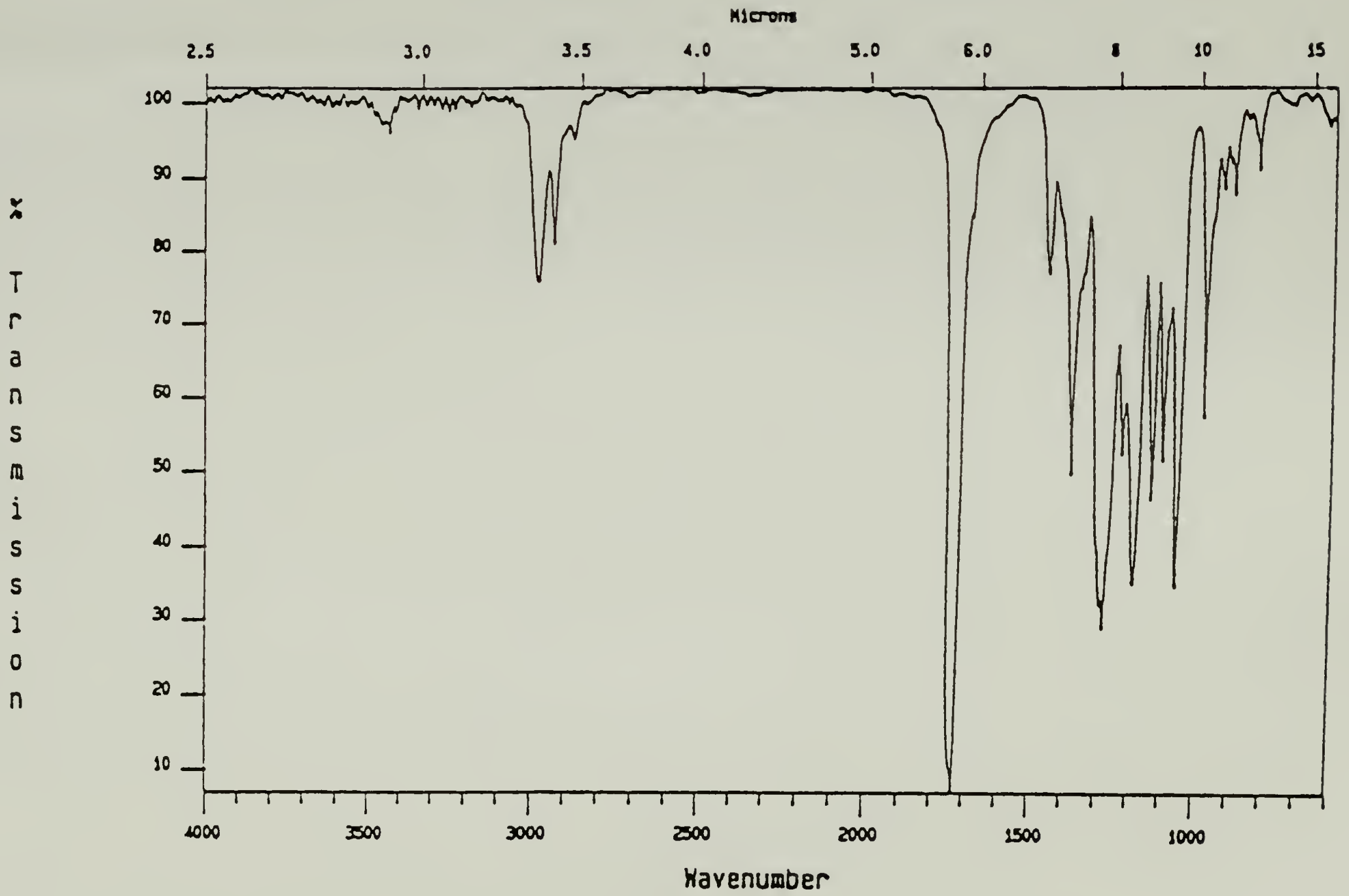


Figure 2.13 FTIR spectrum of the synthetic P([R,S]-HB) using the catalyst EAO.

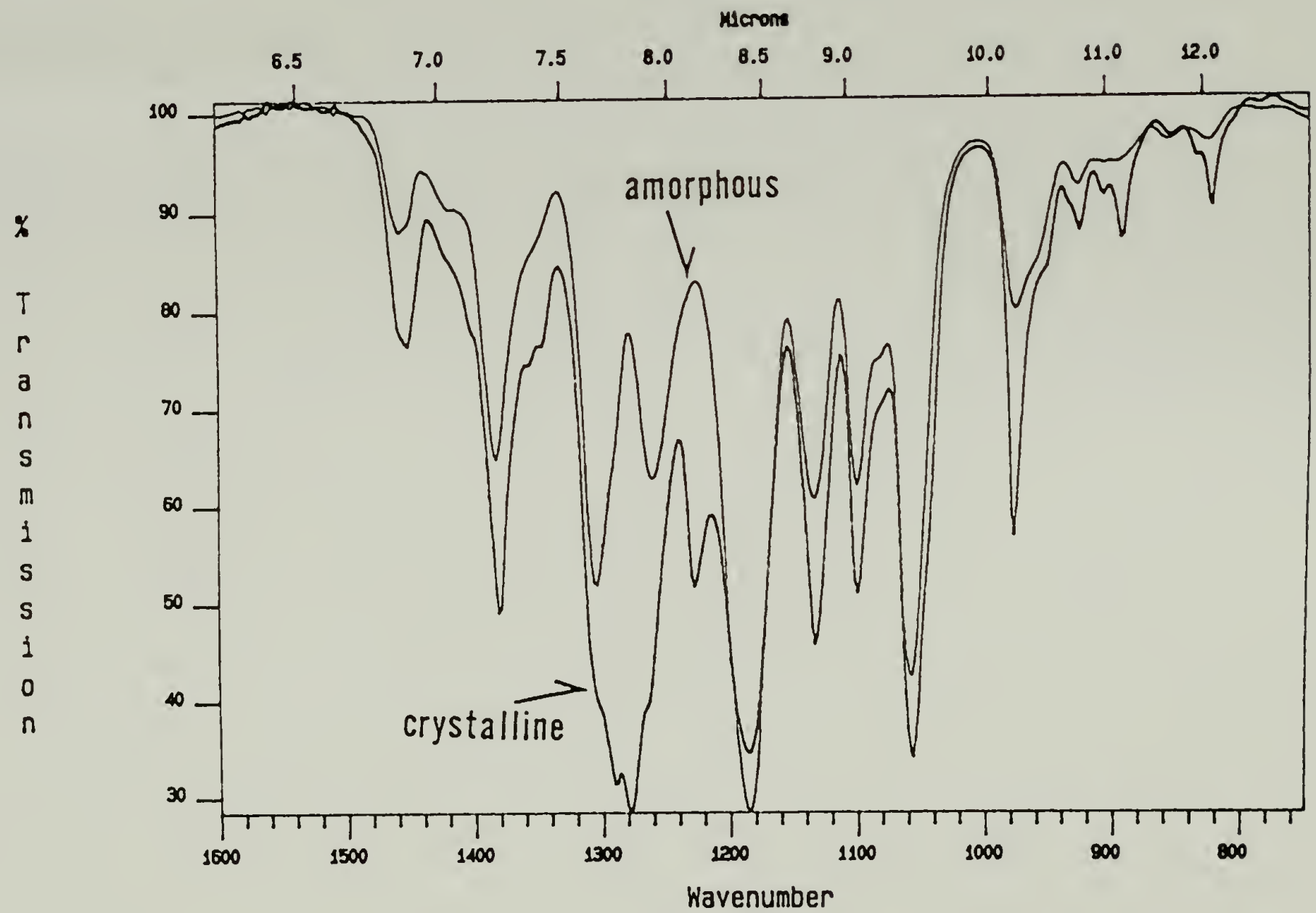


Figure 2.14 Expansions of the FTIR spectra of the crystalline and amorphous P([R,S]-HB) synthesized with the catalysts EAO and $ZnEt_2/H_2O$, respectively.

result is displayed in Figure 2.14-b for an amorphous polymer synthesized with the $ZnEt_2/H_2O$ catalyst. This polymer has a doublet peak with a medium absorption at the same position. Differences between the crystalline and amorphous polymers can also be seen at wavelengths of 1460, 1390, and 980 cm^{-1}. The absorptions from the crystalline polymers are always stronger and sharper, except for that at 1190 cm^{-1}.

It is evident from the results of DSC, ^{13}C NMR and FTIR that the acetone-insoluble fraction of the synthetic P([R,S]-BL) is quite close to natural origin PHB in crystallinity and stereoregularity.

No important differences were observed between the "*In-situ*" and the EAO catalyst from the data shown in Table 2.2-b, but the latter resulted in a better experimental reproducibility and higher polymer yields. The highest yield was achieved on Polymer 7 by taking 60 days instead of 14 days for the polymerization reaction. Hence, longer times are recommended for the polymerization of ß-BL because no molecular weight differences were observed between this sample and others (in Table 2.2-b).

The bimodal distribution of the polymers, especially those of the AcAc and the acetone-insoluble fractions, indicated that there were at least two different active sites in the aluminum-water catalyst system. This behavior is also the basis for the formation of two fractions of different crystallinities, a highly crystalline PBL fraction of high molecular weight and a fraction with low crystallinity and low molecular weight.

(ii) $ZnEt_2/H_2O$ (1:0.6) and TPPAlCl Catalysts The results of the polymerizations of ß-BL using the $ZnEt_2/H_2O$ and TPPAlCl catalysts are shown in Table 2.4 and Table 2.5, respectively. Higher polymer yields, between 90 to 98%, were obtained compared to the 40% yields in the Al-water catalysts. The PBL samples formed with above two catalysts were amorphous and atactic[13-14] determined by the FTIR spectrum in Figure 2.14-b as well as the ^{13}C NMR spectrua of the expanded carbonyl carbon regions in Figure 2.12-c and d.

The living character of TPPAlCl catalyst in the polymerization of ß-BL was previously reported by Inoue and coworkers.[23-25] The values of molecular weights of Polymer 11 and 12 were 3 to 4 times lower than the expected values, although a linear relationship was obtained between the molecular weight of polymers and the molar ratio of monomer to TPPAlCl catalyst, as shown in Figure 2.15 and the formula below. A coefficient number, f, was added in the $\bar{M}_n$ calculation of the formula so to take into accout the living character of the polymerization of ß-BL in this catalyst system.

$$\bar{M}_n = f \cdot M_u \cdot [\text{Monomer}]/[\text{Cat.}]$$

Where M_u is the molecular weight of repeating (BL) unit and f is a number (less than 1) related to the efficiency of the polymerization; f was 1/3 to 1/4 in this study.

Table 2.4 The polymerization of [R,S]-ß-BL & BML using the catalyst $ZnEt_2/H_2O$ (1.0/0.6) and the polymer characterization

Sample	R[e]	mole% Cat./Monomer	Yield[c] %	$\bar{M}_w$ [d] $\bar{M}_n$ ($\bar{M}_w/\bar{M}_n$)	Monomer Feed[a] BL:BML Polymer Comp[b] HB:BM
9	CH_3	1.0	90	<u>100,000</u> 70,000 (1.43)	<u>100:0</u> 100:0
10	CH_3	3.4	90	<u>46,000</u> 30,000 (1.53)	<u>100:0</u> 100:0
30	CH_3/COOBz	1.4	90	<u>41,000</u> 26,000 (1.60)	<u>82:18</u> 85:15
31	CH_3/COOBz	1.4	90	<u>38,000</u> 22,000 (1.70)	<u>73:27</u> 74:26
32	CH_3/COOBz	1.4	85	<u>9,000</u> 5,000 (1.80)	<u>60:40</u> 54:46

a. BL:BML data present in mole% in each monomer.

b. HB:BM data present in mole% in each unit from ^{1}H-NMR.

c. Polymerizations were carried out at 60°C for 7 days (homopolymers) and 14 days (copolymers).

d. Molecular weights were determined by GPC in $CHCl_3$, at 25°C.

e. R is the ß-substituted group.

Table 2.5 The polymerization of BL and BML using the catalyst TPPAlCl and polymer characterization

Sample	(R)	mole% Monomer/Al	Yield[c] %	$\bar{M}_w$ / $\bar{M}_n$ ($\bar{M}_w/\bar{M}_n$)[e]	Monomer Feed[a] BL:BML Polymer Comp[b] HB:BM
11	CH_3	900	95	33,000 21,000 (1.60)	100:0 100:0
12	CH_3	460	95	16,000 12,000 (1.37)	100:0 100:0
20	COOBz	720	98	22,000 16,000 (1.38)	0:100 0:100
21	COOH	--	--	14,000 10,000 (1.40)	--
33	CH_3/COOBz	870	98	21,000 15,000 (1.40)	91:09 90:10
34	CH_3/COOBz	760	95	17,000 13,000 (1.33)	83:17 82:18
35	CH_3/COOBz	570	95	15,000 10,000 (1.50)	82:18 83:17

a. BL:BML data present in mole% in each monomer.

b. HB:BM data present in mole% in each unit from ^{1}H-NMR.

c. Polymerizations were carried out at 60°C for 60 days.

d. The polymerization was carried out at 60°C for 90 days.

e. Molecular weights were determined by GPC in $CHCl_3$, at 25°C.

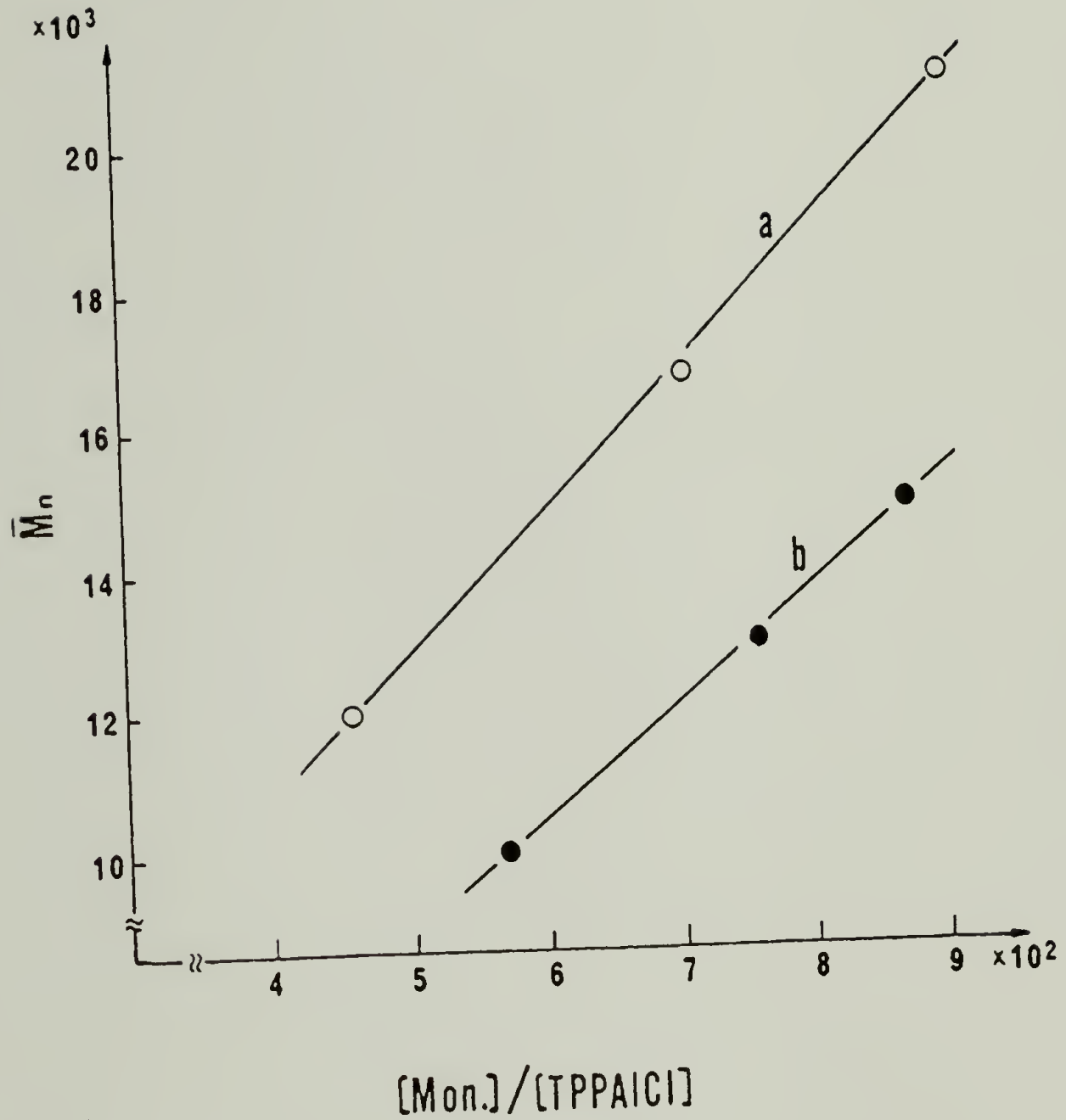


Figure 2.15 Relationship between M_n and ratio of [Mon.]/[TPPAlCl] in the
(a) homopolymerization of β-BL;(○)
(b) copolymerization of β-BL and BML.(●)

2.1.3.3 Hopolymerization of BML

The results of BML polymerization using the aluminum-water catalysts are summarized in Table 2.6. The acetone-insoluble fractions, which contain crystalline PBML, had the molecular weight ($\overline{M}_w$) ranging from 300,000 to 400,000, and the values of $\overline{M}_w/\overline{M}_n$ ranging from 6 to 15. The DSC thermogram recorded on the acetone-insoluble fraction of Polymer 17, as shown in Figure 2.16, clearly indicated the glass transition, the exothermic peak due to crystallization, and the endothermic peak due to melting.

It is known from the previous anionic polymerizations of BML[30-32] that racemic PBML was amorphous, and the optically active polymer was crystalline, having a ΔH_m of 12.5 cal/g and a T_m at 190°C. The acetone-insoluble fractions of Polymer 13-19 synthesized from racemic BML showed the ΔH_m values of 6-7 cal/g at 186-189°C, in Table 2.6. This results suggests that these PBML fractions contain stereoregular chain blockes over a sufficient long length to allow the formation of a crystalline region.

The slightly depressed T_m (from 190°C) and the reduced ΔH_m value from 12.5 cal/g are likely due to the effect of stereo-irregular chain segments acting as crystalline impurities. One investigation carried out by Guerin and coworkers indicated that a mixture of stereoisomers PBML of 70:30 [S]:[R]-BML, which had stereochemical configurations randomly arranged along the chains, had a 50°C depression in T_m relative to pure P([S]-BML).[33] Examples of other poly(ß-substituted-ß-propiolactones) which show this type of behavior have also been given.[34]

Table 2.6 The polymerization of [R,S]-BML using the aluminum-water catalysts

(a) The homopolymerization of [R,S]-BML using the catalysts derived from the reaction of R_3Al and H_2O.

Sample	cat.[b]	polymztn time (days)	molaro ratio H_2O/R_3Al[a]	mol % Al/monomer	yield crude (%)	yield after AcAc treatment (%)	yield of acetone-insol fractn (%)	
							from monmer	from AcAc prod
13	In situ	7	1.45	6.0	24	18	12	(67)
14	In situ	7	1.46	6.7	23	17	12	(71)
15	In situ	7	1.0	4.0	8	6	3	(50)
16	EAO	14	1.0	4.1	12	10	8	(80)
17	EAO	14	1.0	3.4	17	14	8	(57)
18	MAO	14	1.0	4.0	16	14	8	(57)
19	MAO	14	1.0	4.3	20	16	8	(50)

[a] Samples 13-17 R=Et, samples 18,19 R=Me

[b] The in situ catalyst was prepared directly in the polymerization ampule, EAO is ethylalumoxane ($[AlEt\text{-}O\text{-}]_n$), MAO is methylalumoxane ($[AlMe\text{-}O\text{-}]_n$)

[c] AcAc is acetylacetone

(b) Characterization of the product fractions in Table 2.6 (a).

Sample	Molecular Weight Determination (GPC)[a]						ΔH_m,[d] cal/g		Peak melting temp, °C	
	AcAc[b] treated prod[c]		acetone-sol fractn		acetone-insol fractn		AcAc treated prod	acetone insol fractn	AcAc treated prod	acetone insol fract
	$\frac{\bar{M}_w}{M_n}$	$(\bar{M}_w/\bar{M}_n)$	$\frac{\bar{M}_w}{M_n}$	$(\bar{M}_w/\bar{M}_n)$	$\frac{\bar{M}_w}{M_n}$	$(\bar{M}_w/\bar{M}_n)$				
13	540,000 / 36,000	(15)	87,000 / 14,000	(6.2)	680,000 / 69,000	(9.9)	4.0	6.3	183	189
14	330,000 / 41,000	(8.0)	64,000 / 16,000	(4.0)	360,000 / 38,000	(9.5)	4.2	5.8	185	189
15	310,000 / 21,000	(15)	45,000 / 8,000	(5.6)	350,000 / 37,000	(9.5)	4.3	5.6	181	186
16	270,000 / 31,000	(8.7)			360,000 / 47,000	(7.7)	4.9	7.1	188	190
17	300,000 / 18,000	(17)	30,000 / 7,500	(4.0)	310,000 / 33,000	(9.4)	4.5	6.9	184	186
18	450,000 / 25,000	(18)	36,000 / 8,000	(4.5)	310,000 / 34,000	(9.1)	3.6	6.2	178	182
19	190,000 / 15,000	(13)	41,000 / 9,000	(4.6)	390,000 / 38,000	(10)	4.1	6.8	183	186

a Eluted with $CDCl_3$ at 25°C; the molecular weight averages were calculated on the basis of polystyrene standards.
b AcAc is actylacetone.
c Partially fractionated product which remained after AcAc treatment.
d Determined by DSC during the first heating scan.

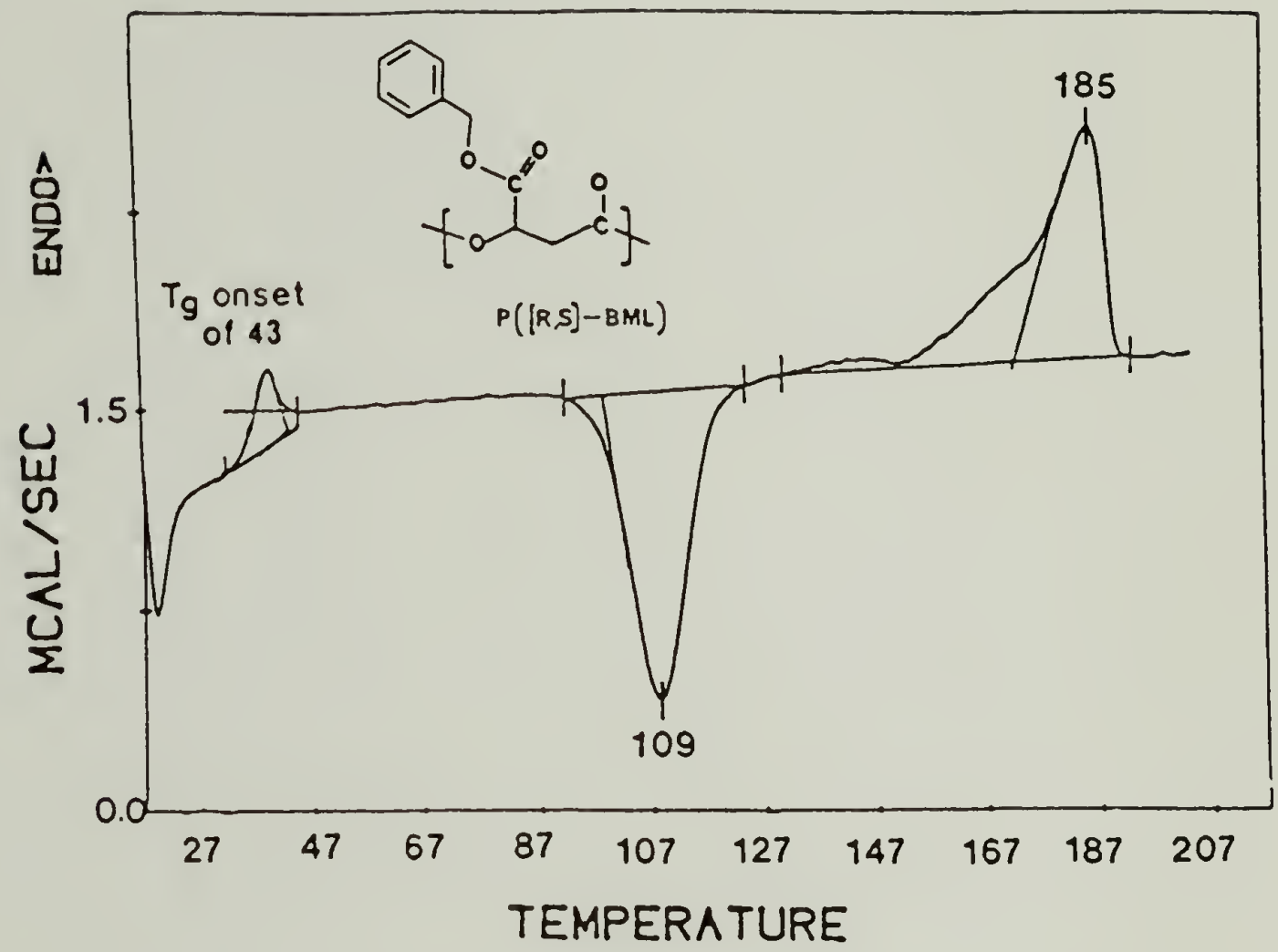


Figure 2.16 DSC thermogram (the second heating scan) of the PBML synthesized using the EAO catalyst.

DSC analysis recorded on the acetone-soluble fractions of Polymer 13-19 did not show the melting transition around 185°C. Instead, a small endothermic transition was often seen at approximately 100°C with a ΔH_m value about 0.5 cal/g. These fractions, therefore, had a low stereoregularity and crystallinity.

The tacticity of the synthetic PBML were studied by ^{13}C NMR spectroscopy. The expanded spectrum of methine carbon 3 showed three major peaks, in Figure 2.17, which were attributed to triad tacticity effects. The peak at the highest field position was identical to that of the isotactic (I) triad.[33] In the acetone-insoluble fraction of Polymer 16, the peak corresponding to the isotactic triad greatly increased in intensity relative to the other triad peaks, as shown in Figure 2.17-b. The acetone-soluble fraction, as shown in Figure 2.17-a, however, does not show this characteristic increase because of the low stereoregularity.

The polymerization of BML with the catalyst TPPAlCl gave an amorphous PBML in a high yield, 98% (Polymer 20 in Table 2.5). In the previous polymerizations of ß-lactones with this catalyst, only those of poly(ß-propiolactone) and PBL were reported.[23-25] The polymerization of BML reported here was, therefore, the first attempt with TPPAlCl as initiator. A polymer with a relatively low molecular weight and a narrow distribution (1.38) was obtained compared to those obtained from the $AlEt_3/H_2O$ catalyst system.

In summary, the ring-opening polymerization of racemic BML was successful in preparing stereoregular PBML using the aluminum-water catalysts. Both the "*In-situ*" catalyst and the

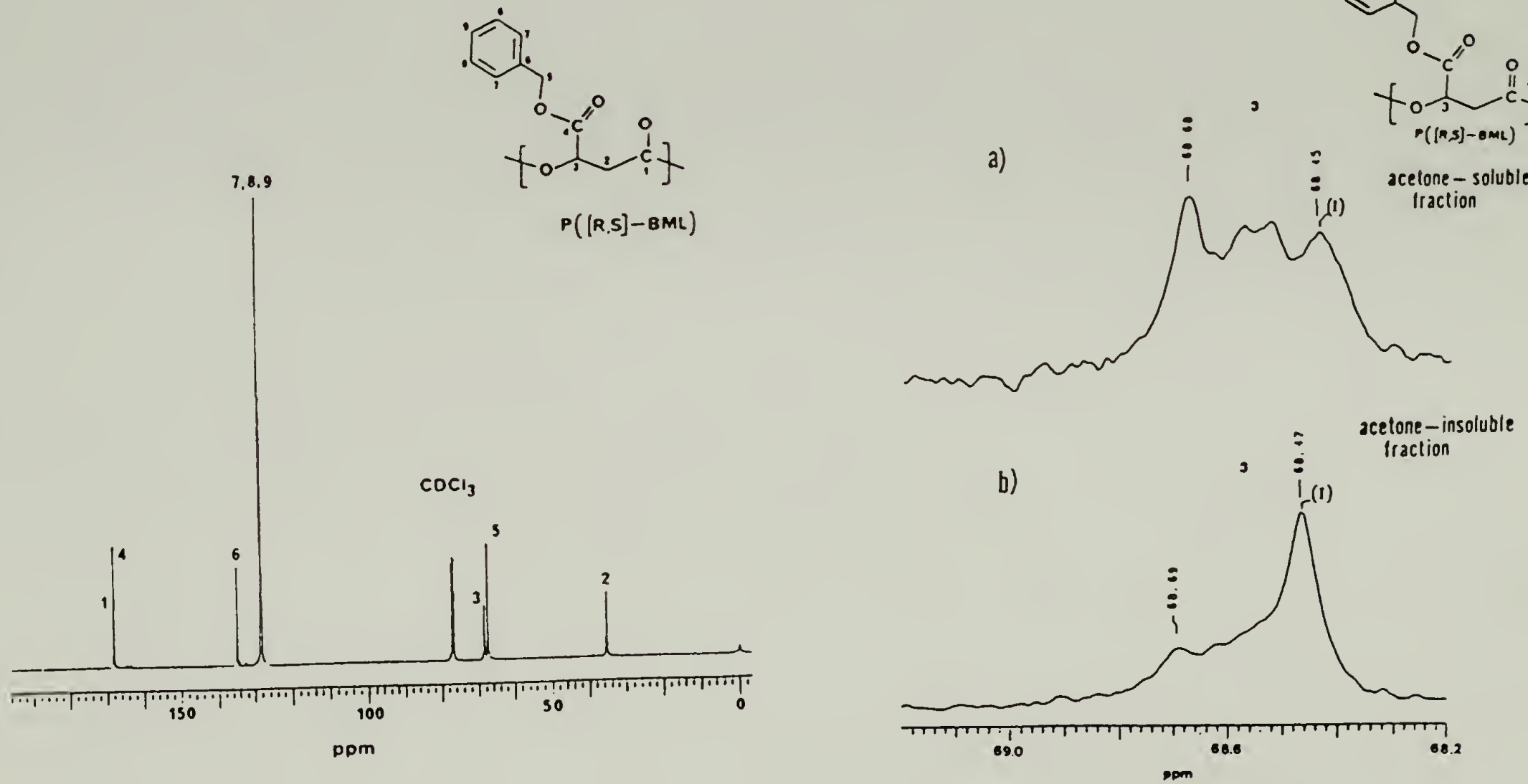


Figure 2.17 ^{13}C NMR spectrum of PBML synthesized using the catalyst EAO and expansions of the methine carbon region.

alkylaluminoxanes produced crystalline polymers with a weight everage molecular weight, $\bar{M}_w$, greater than 300,000. The polymerization with TPPAlCl catalyst resulted an amorphous polymer with an $\bar{M}_w$ of approximately 22,000.

2.1.4 Copolymerization of Racemic BL and BML

The results that all of the premetioned catalysts were capable of polymerizing both BML and BL suggested that the copolymerization of these two monomers with these catalysts could be carried out.

2.1.4.1 Copolymerization with the Aluminum-Water Catalysts

The results of the copolymerizations are summarized in Table 2.7. Longer reaction time was used for these copolymerization reactions relative to the homopolymerization because of a slower progress of the reaction as readily seen by observation of sample flow. When the oligomeric catalysts EAO, MAO and IBAO were used, yields of these copolymers (Polymer 24-29 in Table 2.7) ranged from 20 to 50% after AcAc treatment,[35] but more than 80% of the products were acetone soluble. The highest yield was obtained, on samples 28-29, with the IBAO catalyst, as shown in Table 2.7-a.

The copolymer compositions of HB/BM were determined by integration of the methylene protons, using ^{1}H-NMR spectroscopy. These are clearly seen in Figure 2.18-a, b, and c of the ^{1}H NMR spectra of P([R,S]-BL), PBML and P(HB-co-BM), respectively. The values of copolymer compositions in both the AcAc-treated and the

Table 2.7 Copolymerization of [R,S]-BL and BML using the aluminum-water catalysts

(a) Copolymerization of [R,S]-BL and BML using the catalysts derived from the reaction of R_3Al and H_2O

Sample	cat[b]	polymztn time (days)	molar ratio H_2O/AlR_3[a]	Mole% Al/Monomer	Monomer Feed[c] BL:BML / Polymer Comp.[c] HB:BM	yield crude (%)	yield after AcAc treatment (%)	yield of acetone-sol fractn (%)
22	In situ	27	1.45	6.0	50:50 / 22:78	17	5	-
23	In situ	27	1.00	4.0	80:20 / 70:30	17	3	-
24	EAO	27	1.0	4.0	50:50 / 45:55	15	10	9.2
25	EAO	27	1.0	3.6	32:68 / 36:64	27	23	19
26	MAO	27	1.0	3.8	46:54 / 50:50	26	21	19
27	MAO	27	1.0	4.0	28:72 / 28:72	32	27	23
28	IBAO	27	1.0	4.0	50:50 / 46:54	64	43	34
29	IBAO	27	1.0	4.0	50:50 / 45:55	70	48	43

a samples 22-25 R=Et, samples 26,27 R=Me, samples 28,29 R=i-Bu
b The in situ catalyst was prepared directly in the polymerization ampule, EAO is ethylalumoxane ($[AlEt\text{-}O\text{-}]_n$), MAO is methylalumoxane ($[AlMe\text{-}O\text{-}]_n$), IBAO is iso-butylalumoxane ($[AlBu\text{-}O\text{-}]_n$)
c data presented in mole% of each monomer
d AcAc is acetylacetone

(b) Characterization of the product fractions in Table 2.7 (a).

Sample	Molecular Weight Determination (GPC)[a] AcAc[b] treated prot[c] $\frac{\bar{M}_w}{\bar{M}_n}$ ($\bar{M}_w/\bar{M}_n$)	acetone-sol fractn $\frac{\bar{M}_w}{\bar{M}_n}$ ($\bar{M}_w/\bar{M}_n$)	acetone-insol fractn $\frac{\bar{M}_w}{\bar{M}_n}$ ($\bar{M}_w/\bar{M}_n$)	ΔH_m[d] after AcAc treatment cal/g	Peak Melting temp after AcAc treatment °C	Composition[e] acetone-sol fractn HB:BM	acetone-insol fractn HB:BM
22	$\frac{67,000}{15,000}$ (4.5)	-	-	1.1	153	-	-
23	$\frac{240,000}{37,000}$ (6.5)	-	-	2.0	155	-	-
24	$\frac{200,000}{17,000}$ (12)	$\frac{70,000}{16,000}$ (4.3)	$\frac{600,000}{68,000}$ (8.8)	0.6	150	44:56	-
35	$\frac{270,000}{17,000}$ (16)	$\frac{210,000}{15,000}$ (14)	$\frac{840,000}{120,000}$ (7.0)	0.6	153	32:68	48:52
26	$\frac{400,000}{34,000}$ (12)	$\frac{320,000}{30,000}$ (11)	$\frac{690,000}{62,000}$ (11)	0.3	153	44:56	50:50
27	$\frac{300,000}{17,000}$ (17)	$\frac{140,000}{16,000}$ (9.3)	$\frac{760,000}{68,000}$ (8.8)	0.6	150	28:72	33:67
28	$\frac{230,000}{16,000}$ (6.8)	$\frac{200,000}{11,000}$ (7.7)	$\frac{840,000}{120,000}$ (7.0)	0.4	153	44:56	50:50
29	$\frac{200,000}{23,000}$ (8.7)	$\frac{120,000}{14,000}$ (8.6)	$\frac{460,000}{72,000}$ (6.4)	1.2	160	43:57	65:35

a eluted with $CDCl_3$ at 25°C, the molecular weight averages were calculated based on polystyrene standards
b AcAc is acetylacetone
c partially fractionated product which remained after AcAc treatment
d determined by DSC during the first heating scan
e data presented in mole% of comonomer units

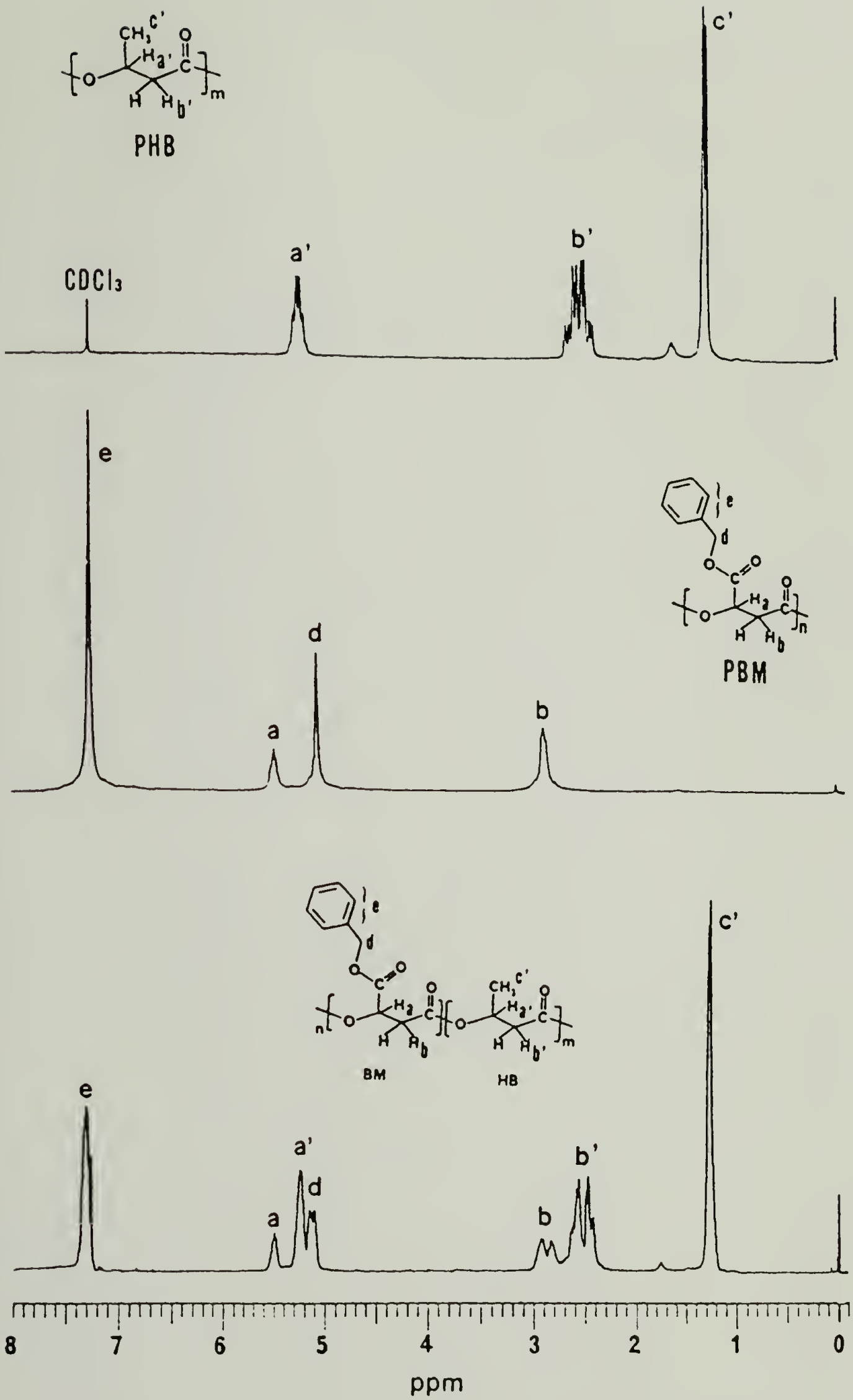


Figure 2.18 ^{1}H NMR spectra of PHB, PBML and P(HB-co-BM).

acetone-soluble fractions, as displaced in Table 2.7, closely approached the ratio of monomer feed used. This result, which facilitates the composition control in the copolymer system, was not anticipated for two reasons: firstly, ß-BL and BML may have very different reactivities due to the steric and electronic differences in their monomer structures; secondly, the copolymerization had a low yield, less than 50%.

The DSC thermogram recorded for these AcAc-treated copolymers showed a low melting temperature, ranging from 140 to 170°C, and a small ΔH_m value around, 1.0 cal/g. The lower intensity of ΔH_m, compared to those of crystalline homopolymers of PBL and PBML, suggest that the copolymers contain primarily random comonomer distributions. This behavior is not surprising because the comonomer units have very different pendant groups which are likely to impede their crystallization.

The observed melting temperature for these copolymers was on average 9° and 30°C lower than those of the acetone-insoluble fraction of P([R,S]-BL) and PBML, respectively (see Table 2.2-b, 2.6-b and 2.7-b). While the exothermal peak corresponding to the copolymer crystalization at 65°C, as shown in Figure 2.19, was in the same range of the crystallization exothermal peak of P([R,S]-BL), but quite different from that of PBML's. The above results suggest that the small melting and crystallization peaks observed for P(HB-co-BML) copolymers may arise from the polymer chain segments containing somewhat stereo-regular blocks of HB unit, which were enriched in the acetone-insoluble fractions.[36] This

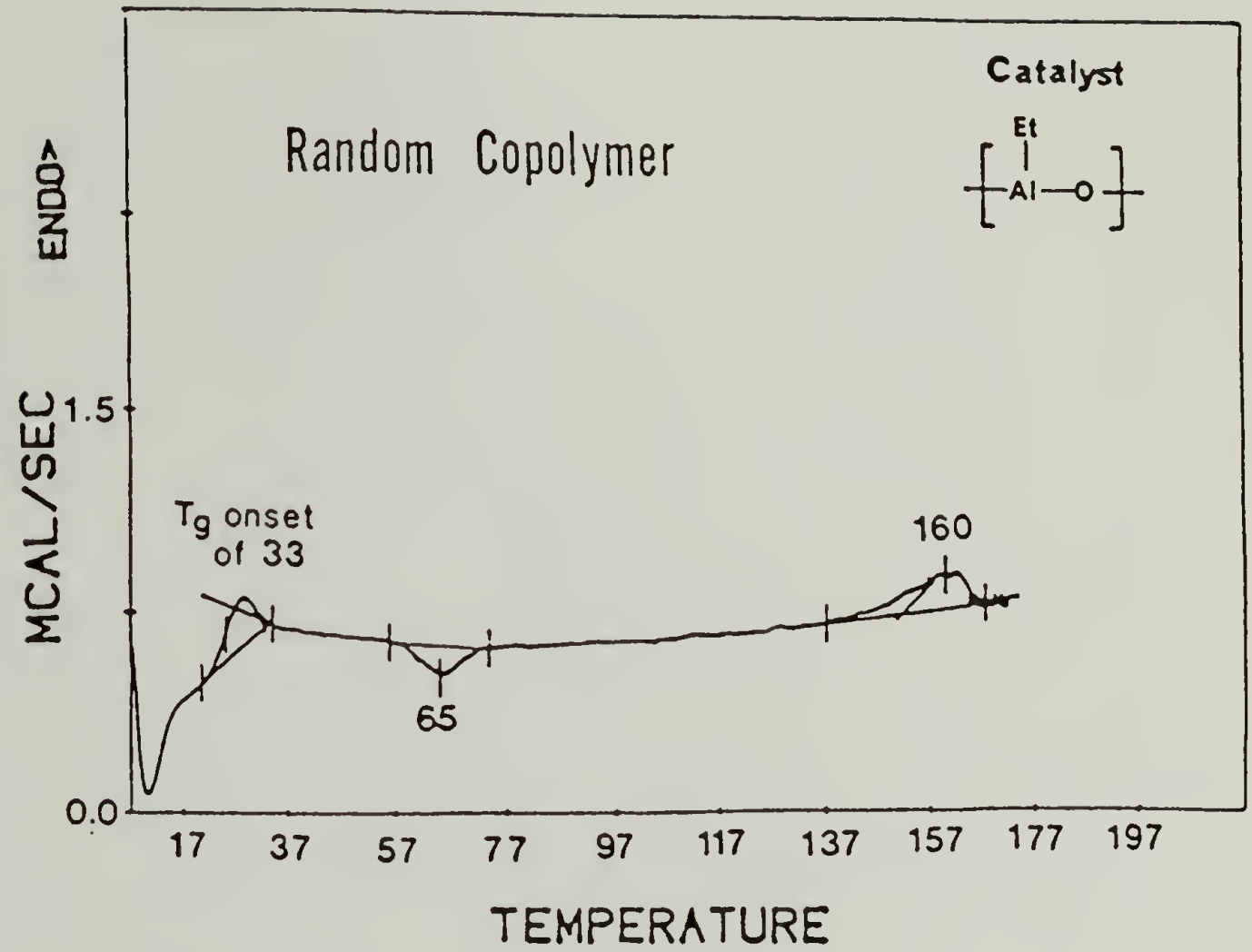


Figure 2.19 DSC thermogram (the 2nd heating scan) of the copolymer synthesized using the EAO catalyst.

assumption was supported by the absence of both melting and crystallization thermal transitions in acetone-soluble fractions. In contrast, higher melting temperatures of 156-160°C and higher values of ΔH_m ($\geq$ 4 to 6 cal/g) were observed in the acetone-insoluble fractions obtained from the IBAO catalyst.

It is obvious from above results that the IBAO is a better catalyst for producing the copolymer having higher stereo-regularity and higher yield. The difference in the ability of these aluminum-water catalysts, especially those aluminoxanes with different alkyl substitutions, to yield high molecular weight copolymer, is probably associated with their thermal stabilities. The smaller the alkyl group is attched to the catalyst metal, the easier it is to be removed by forming either a corresponding alkane in the presence of water or a free trialkyl aluminum in high temperature. The fact that this difference did not obviously observed in the homopolymerization reactions probably because the reaction time used were not long enough to observe the effect. A similar explanation was given for the Al/Zn dimetallic μ-Oxoalkoxide catalyst, $R_2Al\text{-}O\text{-}Zn\text{-}AlR_2$, where isopropanol was replaced by n-butanol to stabilize the catalyst product. The latter catalyst had a better reproducibility in producing crystalline poly(caprolactone).[33-34]

GPC chromatographs of the copolymers showed broad distributions with these AlR_3/H_2O catalysts (Figure 2.20), especially for those copolymers synthesized with the "*In-situ*" catalyst. This result suggests a extreme heterogenity of the

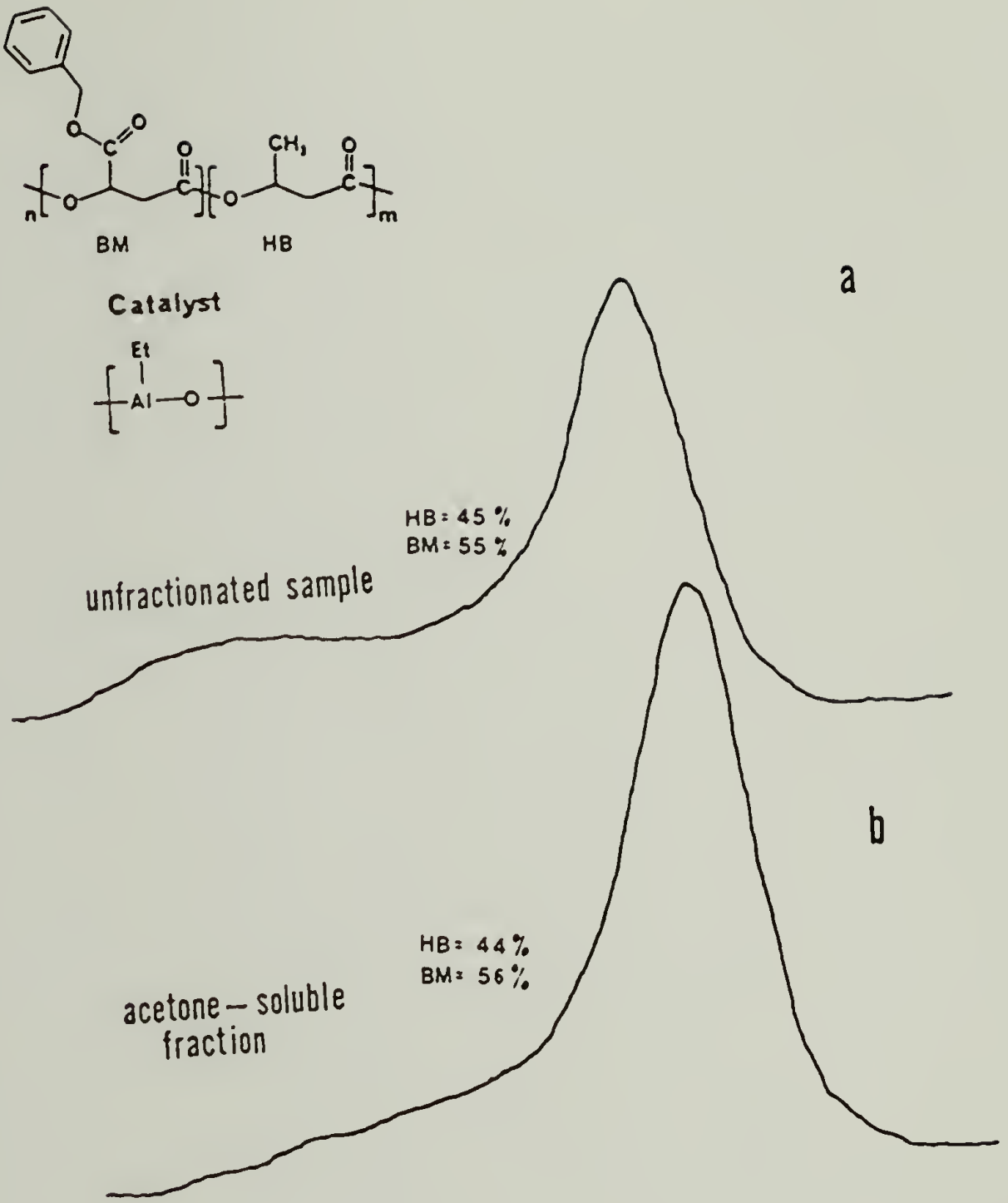


Figure 2.20 GPC chromatography of the copolymer synthesized using the EAO catalyst.
(a) the unfractionated (AcAc treated) sample;
(b) the acetone-soluble fraction (≥80% of the a)

samples.

2.1.4.2 Copolymerization with the Catalysts $ZnEt_2/H_2O$ and TPPAlCl

Amorphous copolymers were produced, by using the $ZnEt_2/H_2O$ and TPPAlCl catalysts, in the high yield of 90 to 98%. Therefore, very good matches between monomer feeds and copolymer compositions were obtained in the above two catalyst systems, as shown in Table 2.4 and 2.5.

An interesting result observed in the copolymerization with the $ZnEt_2/H_2O$ catalyst was that the molecular weight of copolymers dereased when the molar ratio of BML to BL increased (see Table 2.6). It was reported previously by Araki and coworkers,[38-40] that the EAO and the $ZnEt_2/H_2O$ catalysts behave quite differently in the ring-opening polymerization of ß-(2-acetoxyethyl)-ß-propiolactone, as shown in Figure 2.21. The Al catalyst produced a polymer enriched by poly(ß-ester) structure as in the normal case, but the Zn catalyst gave a polymer dominated by poly(δ-ester) structure.[38] As the key to the discrepancy of catalytic behaviors in the Zn- and Al-catalysts, it has been noted that the Zn atom coordinates predominantly with the linear chain ester group but the Al atom prefers the lactone-ring ester group.[41]

In the polymerization of ß-BL and ß-BML with the Zn-catalyst, the ring-opening reaction on the lactone was the only choice for chain initiation and propagation. However, the chain transfer or/and termination were possible by coordination of the catalyst with the linear benzoxy substituted group in side chain of

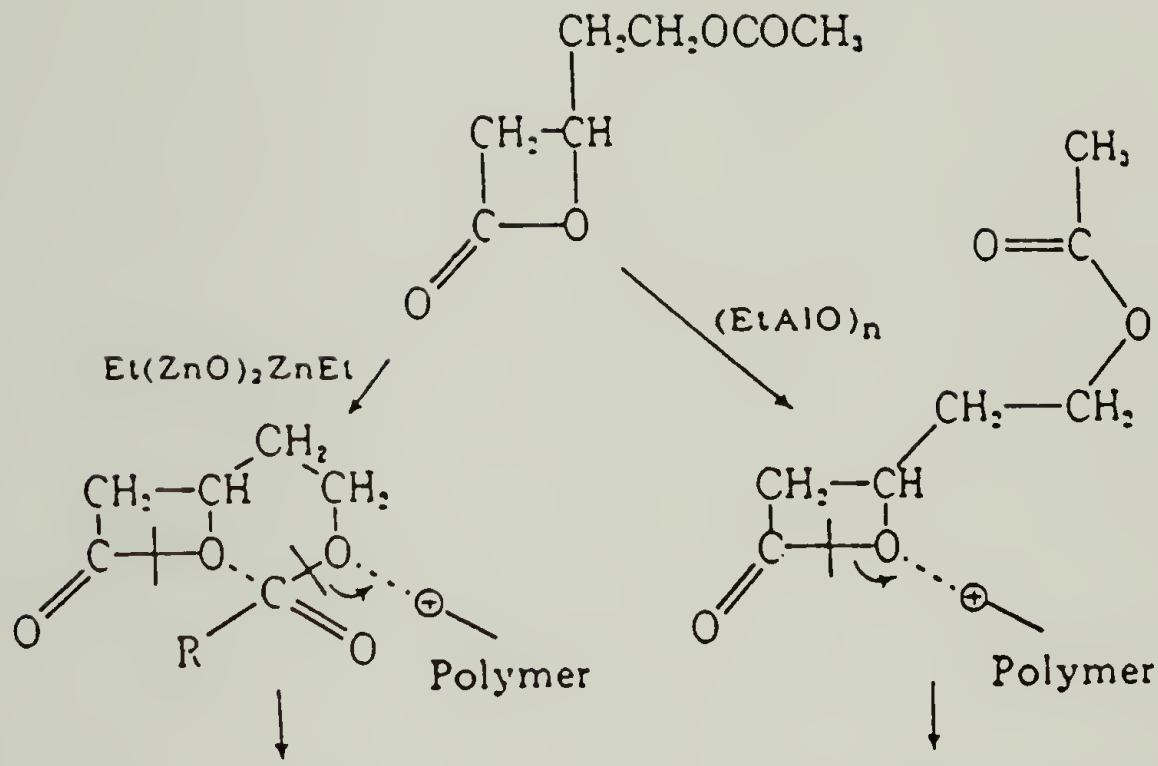


Figure 2.21 Two polymerization routes of β-(2-acetoxyethyl)β-propiolactone.

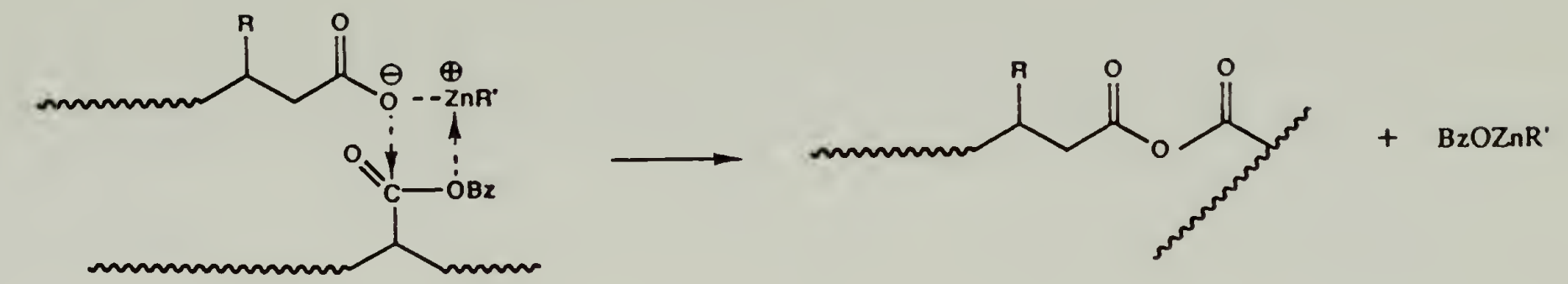
BML unit, as shown in Figure 2.22. It is not surprising, therefore, that the molecular weight decreased sharply when the molar content of BML rose from 27 to 40% (see Table 2.4), since there were more opportunities for the chian transfer or/and termination. This phenomenon was not observed in the copolymerization with the Al-catalyst because aluminum is more oxygen- and electrophilic than zinc, so has a strong coordination on the lactones. Conclusively, there were some difficulties in using the $ZnEt_2/H_2O$ catalyst to obtain high molecular weight copolymer P(HB-co-BML), especially when a high BML composition was needed.

When using the TPPAlCl catalyst, the copolymerizations were carried out at 60°C for 60 days because of the lower polymerization rate. There was a somewhat linear relationship between the molecular weight of polymers and the molar ratio of monomer to catalyst, as discussed previously in Figure 2.16. The catalyst TPPAlCl, however, can not be considered as a good living system for the copolymerization reactions until it is given the coeffience number, f, in the molecular weight calculation, as shown previously (see 2.1.3.2, ii). The molacular weight distribution of the copolymers with this catalyst was approximately 1.3.

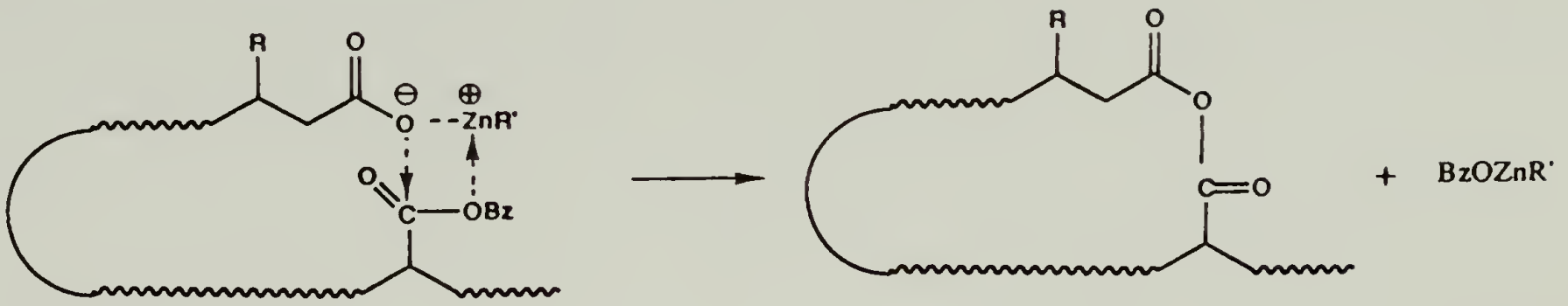
2.1.4.3 Comonomer Sequences of P(HB-co-BM)

The comonomer sequences of P(HB-co-BM) were determined by ^{13}C NMR, as shown in Figure 2.23 and 2.24, the spectra of Copolymer 26 and its methylene expanded region, respectively. In Figure 2.24, the expansion of methylene carbons, the most sensitive

a). Intermolecular transfer:

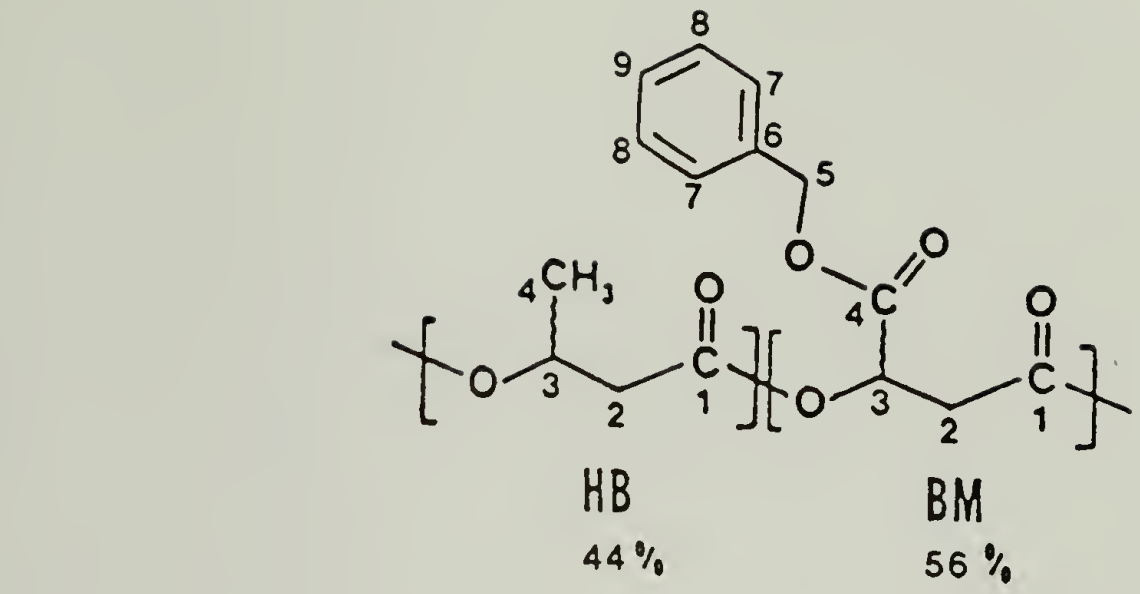


b). Intramolecular transfer:



R= CH_3 or COOBz

Figure 2.22 The chain transfer reactions assumed in the polymerization of BML using the Et_2Zn/H_2O catalyst.



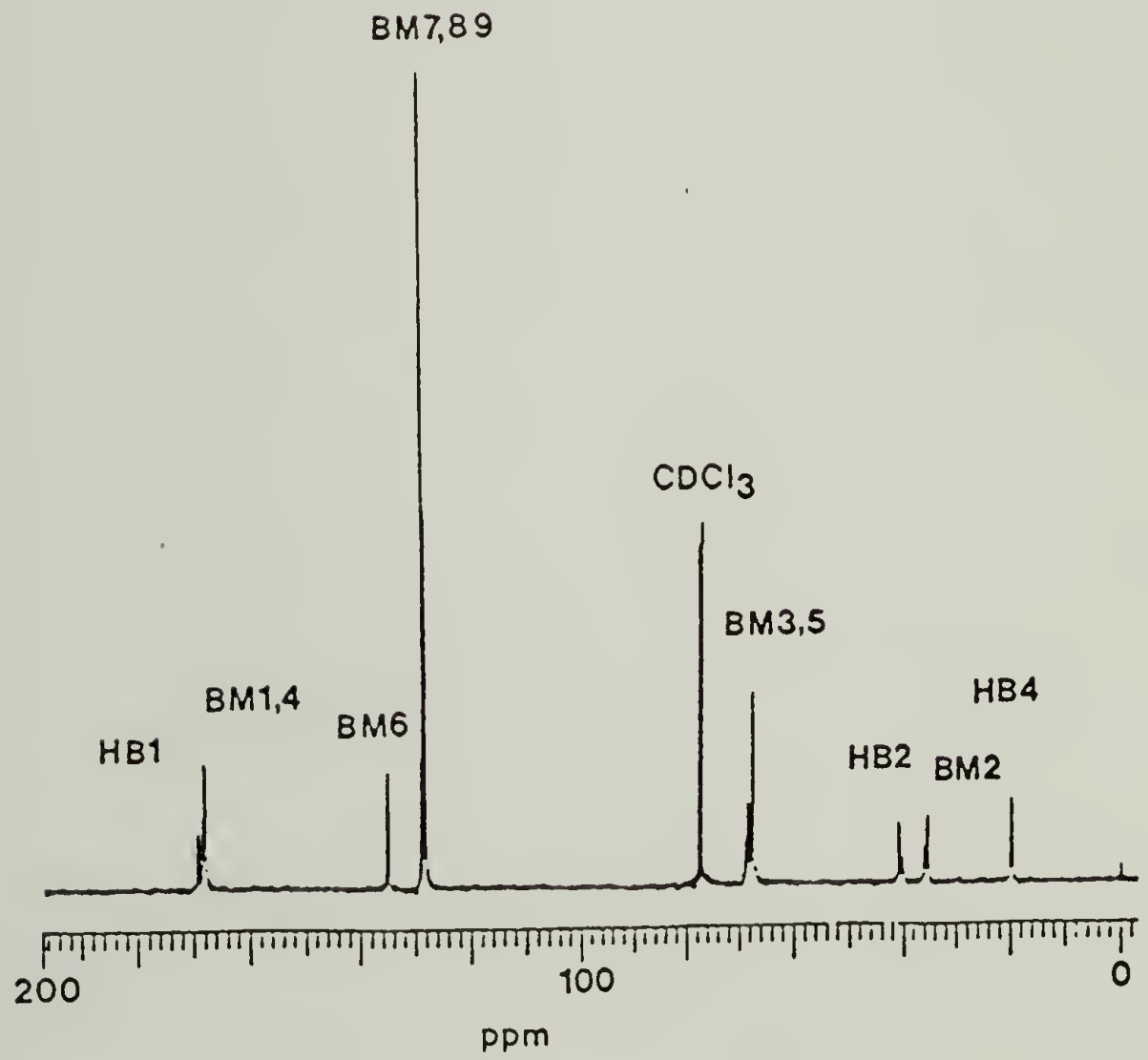
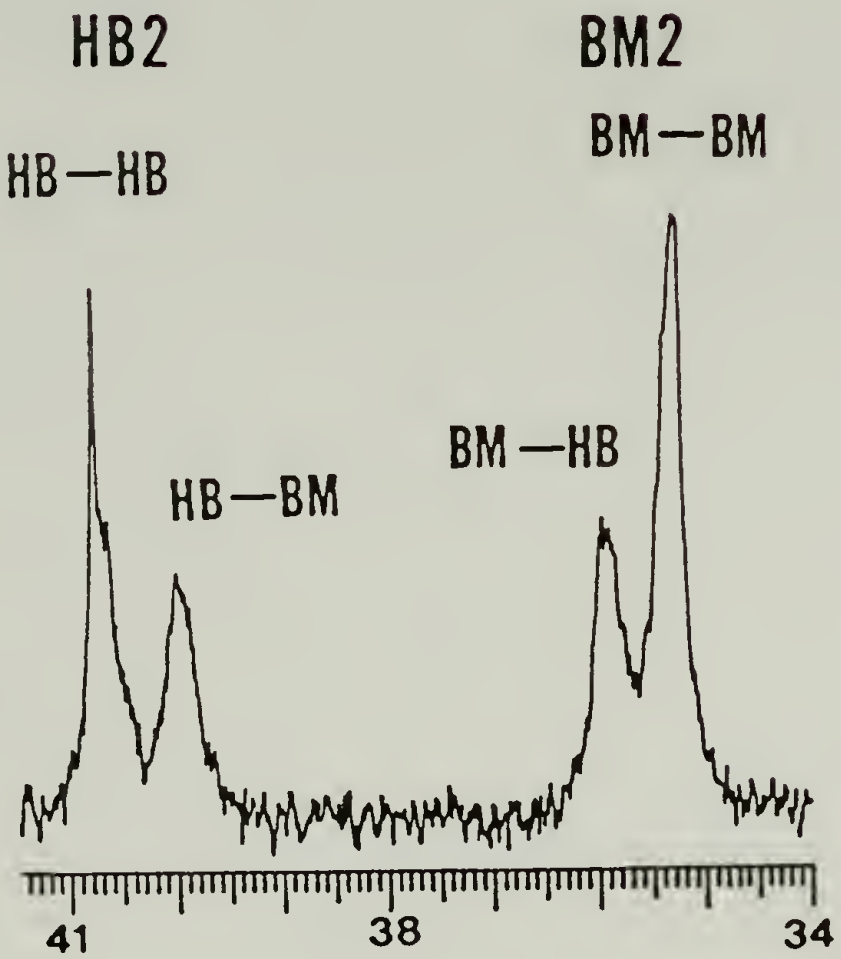


Figure 2.23 ^{13}C NMR spectrum of P(HB-co-BM) synthesized using the catalyst EAO.



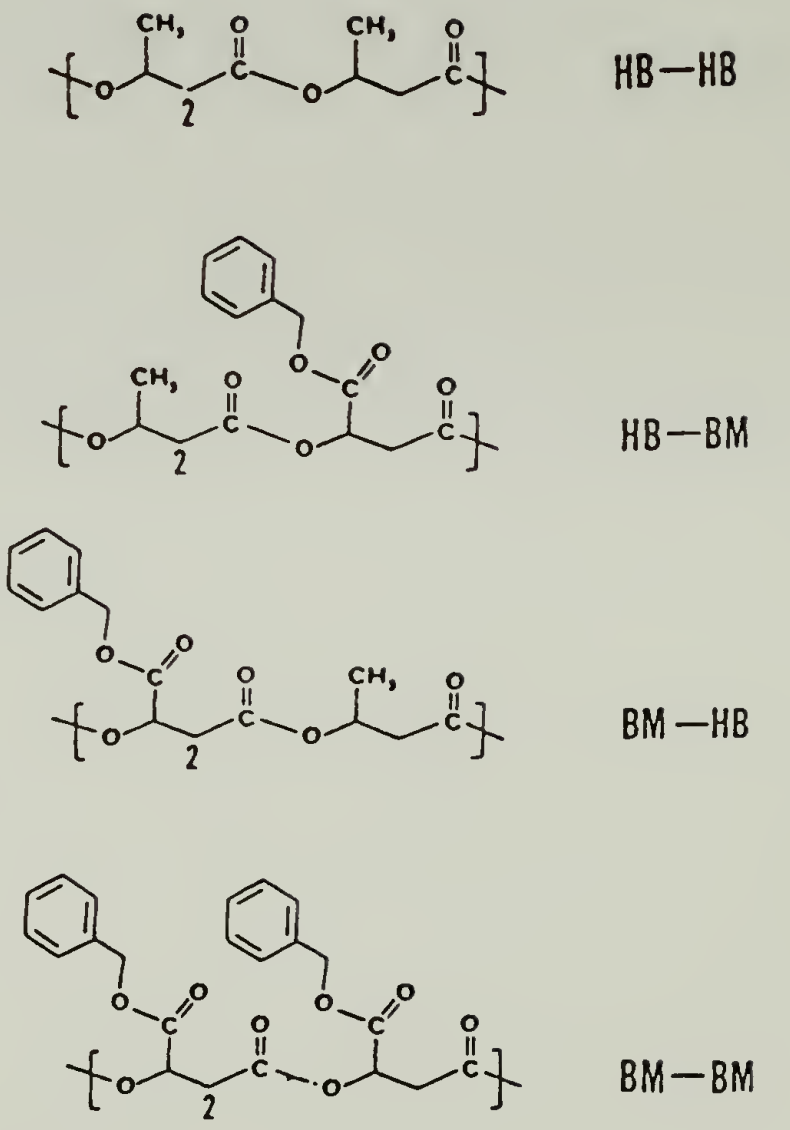


Figure 2.24 Expansion of the methylene carbon reigon of Figure 2.23 and the corresponding comonomer diad sequences.

region in the copolymer structure, were shown along with the peak assignments for the comonomer diad sequences. These assignments were made by mixing the copolymer with PBML and PBL, respectively. In the former case, there was an increase in the upfield signal, allowing the assignment of BM-BM comonomer diad sequence. While in the latter case, an increase in the downfield signal was assigned to the HB-HB diad sequence. Another two assignments of BM-HB and HB-BM diad sequences were made by assuming a relatively small change of chemical shift both for BM-BM/BM-HB and HB-HB/HB-BM (see Figure 2.24). All these peak assignments were used for quantitative analysis on the relative fractions of comonomer diad sequences, as shown in Table 2.8.

If a bernoullian or random statistical copolymerization was assumed, the comonomer diad fractions can be calculated with the knowledge of F_{HB} (defined as the mole fraction of HB units in polymer) by using the following equations:[37]

$$[HB\text{-}HB] = F_{HB}^{\,2} \qquad (1)$$

$$[HB\text{-}BM] = [BM\text{-}HB] = F_{HB}(1 - F_{HB}) \qquad (2)$$

$$[BM\text{-}BM] = (1 - F_{HB})^2 \qquad (3)$$

Where, F_{HB} was determined by ^1H NMR spectroscopy by intergration. The values of calculated comonomer diad sequences (using above equations), as shown in Table 2.8, are compared with the observed values for those samples synthesized with the different catalysts. The observed values were obtained by cutting and weighing the

Table 2.8 Experimental and calculated comonomer diad fractions of P(HB-co-BM).

Sample	catalyst	polym comp[c] HB:BM	diad sequence HB-HB Observed[a] (calcd)[b]	HB-BM Observed[a] (calcd)[b]	BM-HB Observed[a] (calcd)[b]	BM-BM Observed[a] (calcd)[b]
25 - acetone-sol fractn	EAO	32:68	0.18 (0.10)	0.14 (0.22)	0.23 (0.22)	0.45 (0.46)
25 - acetone-insol fractn	EAO	49:51	0.41 (0.24)	0.08 (0.25)	0.18 (0.25)	0.33 (0.26)
27 - AcAc treatment	MAO	28:72	0.14 (0.08)	0.14 (0.20)	0.14 (0.20)	0.58 (0.52)
27 - acetone-Sol fractn	MAO	28:72	0.14 (0.08)	0.14 (0.20)	0.14 (0.20)	0.49 (0.52)
29 - acetone-sol fractn	IBAO	43:57	0.26 (0.19)	0.17 (0.25)	0.22 (0.25)	0.35 (0.33)
29 - acetone-insol fractn	IBAO	65:35	0.67 (0.43)	0.03 (0.23)	0.06 (0.23)	0.24 (0.12)
32 - whole sample	$ZnEt_2/H_2O$	54:46	0.36 (0.30)	0.24 (0.25)	0.24 (0.25)	0.16 (0.20)
33 - whole sample	TPPAlCl	90:10	0.78 (0.81)	0.11 (0.09)	0.08 (0.09)	0.03 (0.01)

[a] relative peak areas of the methylene carbon (2) for the comonomer diad sequences observed in ^{13}C NMR spectra
[b] calculated values from equations (1)-(3) assuming a perfectly random distribution
[c] data presented in mole% of comonomer units
[d] AcAc is acetylacetone

respective peaks of comonomer diad fractions in the BM2 and HB2 signals (Figure 2.24).[41]

The comparison of the results between the calculated and observed values can be concluded in following points: (a) Amorphous copolymers synthesized with the $ZnEt_2/H_2O$ and TPPAlCl catalysts were statistically random in the comonomer distributions; (b) For the copolymers synthesized with the aluminoxanes, a total random or bernoullian distribution between HB and BM was not observed althgh a better agreement between observed and calculated comonomer diads occured in the acetone-soluble fractions. When a BM unit was at end of a growing chain, it reacted with a subsequented BM or HB unit with little selectivity, but when a HB unit was at terminal of a growing chain, it preferably add another HB unit than a BM unit. That is why the observed values of HB-HB diad fraction were considerably larger than the calculated random distrabutions, especially in those acetone-insoluble fractions. This indicates, in some extents, a copolymer with several HB and BM blocks, and it was especially true for the copolymer with the IBAO catalyst.

In summary, the copolymers with controlled BM/HB comonomer compositions were synthesized by using the catalysts of aluminoxanes (including MAO, EAO and IBAO), $ZnEt_2/H_2O$ and TPPAlCl. The latter two catalysts are more suitable for synthesis of the random amorphous copolymer P(BL-co-BM), in a relatively high yield, but improvements are needed to increase molecular weight of these polymer products. The usage of aluminoxanes is

successful than that of the "*In-situ*" catalyst in the synthesis of high molecular weight copolymers with two different fractions. These fractions are the acetone-soluble fraction with some extent random distribution and the acetone-insoluble fraction with several stereoblocks of HB sequences.

2.2 Stereochemical Study on the Ring-Opening Polymerization of ß-Butyrolactone

2.2.1 Synthesis of Optically Active [S]-ß-BL

Optically active ß-alkyl-ß-propiolactones can be synthesized, in the presence of chiral catalysts, by the reaction of C-C bond-forming between carbonyl compound and ketene, as described previously in 1.7.[42-45] However, the chemical and enantiomeric yields of these lactones were strongly dependent upon the polarity of a carbonyl group and the effectiveness of a chiral catalyst.[44] The optical purities of the ß-lactones synthesized in the above manner were usually in the range of 45%[44] to 100% ee.[42-43]

[R] and [S]-butyrolactones (BL) were previously prepared through a classical resolution of diastereomeric salts.[46-48] [R,S]-ß-bromobutyric acid reacted with α-(1-naphthyl)ethyl amine to form either [R] or [S]-ß-bromobutyric acid. The ß-bromobutyric acids were then converted to their respective lactones to obtain samples of the desired stereochemistry. The optically active BL, synthesized in above manner, had optical purities ranging from 73%[47-48] to greater than 97%.[49]

Seebach and co-workers recently reported a synthetic route to [S]-BL with an optical purity of greater than 98% using the chiral precursor P([R]-HB).[50-51] This synthetic route involves the pyrolysis of a cyclic orthocarbonate which degrades thermally, forming the corresponding ß-lactone with an overall yield of 23%.

In this study, [S]-butyrolactone ([S]-BL) was prepared by the synthetic scheme in Figure 2.25, from a readily available chiral precursor, the natural origin P([R]-HB).[52] It has been proven that there are no configuration inversion or racemization in the first four step reactions except the last lactonization where an inversion of configuration occurs.[52-54] The above five step reactions proceeded with an overall yield of 20 wt.%.

As shown in Figure 2.25, [R]-methyl-ß-hydroxybutyrate ([R]-MHB) was prepared by the degradation of natural origin P([R]-HB) through acidic methanolysis. That the procedure did not undergo any racemization has been proven by both the specific rotation[54-56] and the ^{1}H-NMR spectrum in the presence of the europium shift regent. The crude yield of [R]-MHB was increased from 60 to 90% when the reaction time was extended from 18 to 26 hours at reflux temperature.

[R]-MHB was then converted into its benzyl ester (II) which would protect the carboxyl group during the subsequent mesylation reaction. This acid-catalyzed esterification reaction of [R]-MHB with benzyl alcohol proceeded successfully with a yield of 95%.

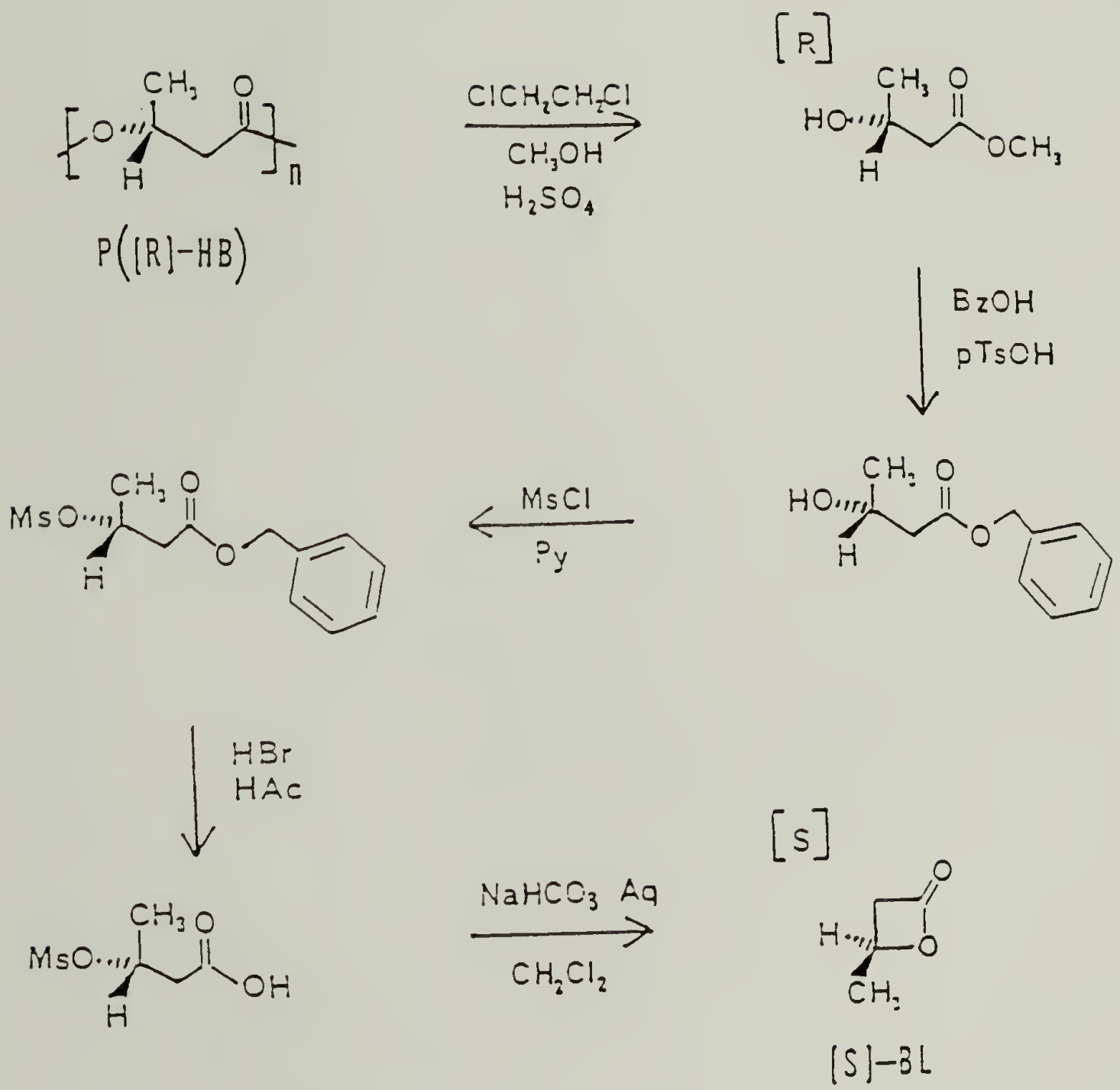
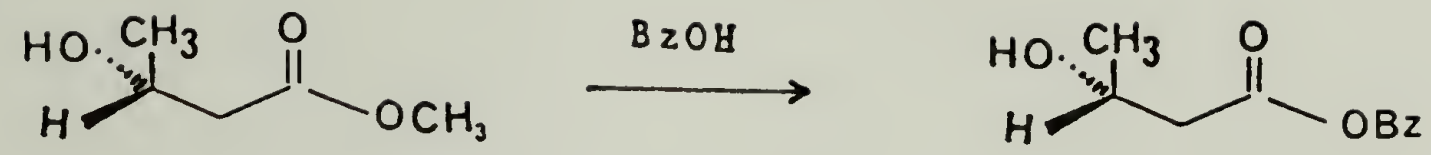


Figure 2.25 A synthetic scheme for the synthesis of [S]-BL from natural origin P([R]-HB).

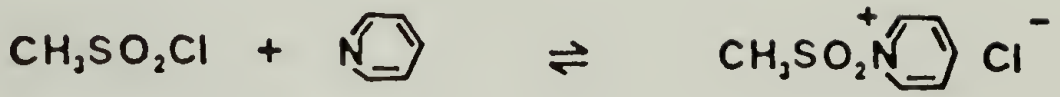


A five fold excess of benzyl alcohol was used to reduce the self-esterification of [R]-MHB, and the methanol formed in the above reaction was removed immediately by azeotropic distillation under reduced pressure. Para-toluenesulfonic acid was used as an effective catalyst in the esterification. Spectroscopic evaluation of [R]-benzyl hydroxybutyrate by infrared and ^{1}H NMR spectroscopy showed that the reaction had occurred without dehydration. No double bond adsorption was observed in these spectra.[32]

Benzyl-[R]-hydroxybutyrate then reacted with mesyl chloride in a ratio of 1:1.3, using methlene chloride as solvent, forming the benzyl [R]-O-mesylbutyrate, III, in a nearly quantitative yield. The reaction was proceeded through an S_N2 displacement,[57] as shown in Figure 2.26, using pyridine as both a nucleophilic catalyst and an acid scavenger. A leaving group of mesylate was used instead of a tosylate because the mesylbutyrate would have a higher solubility in aqueous sodium bicarbonate than the corresponding tosylate compound in the subsequent lactonization reaction.

[R]-O-mesylbutyric acid, IV, was prepared by the debenzylation of benzyl mesylbutyrate with hydrobromic acid

Nucleophilic Catalysis



Nucleophilic Substitution

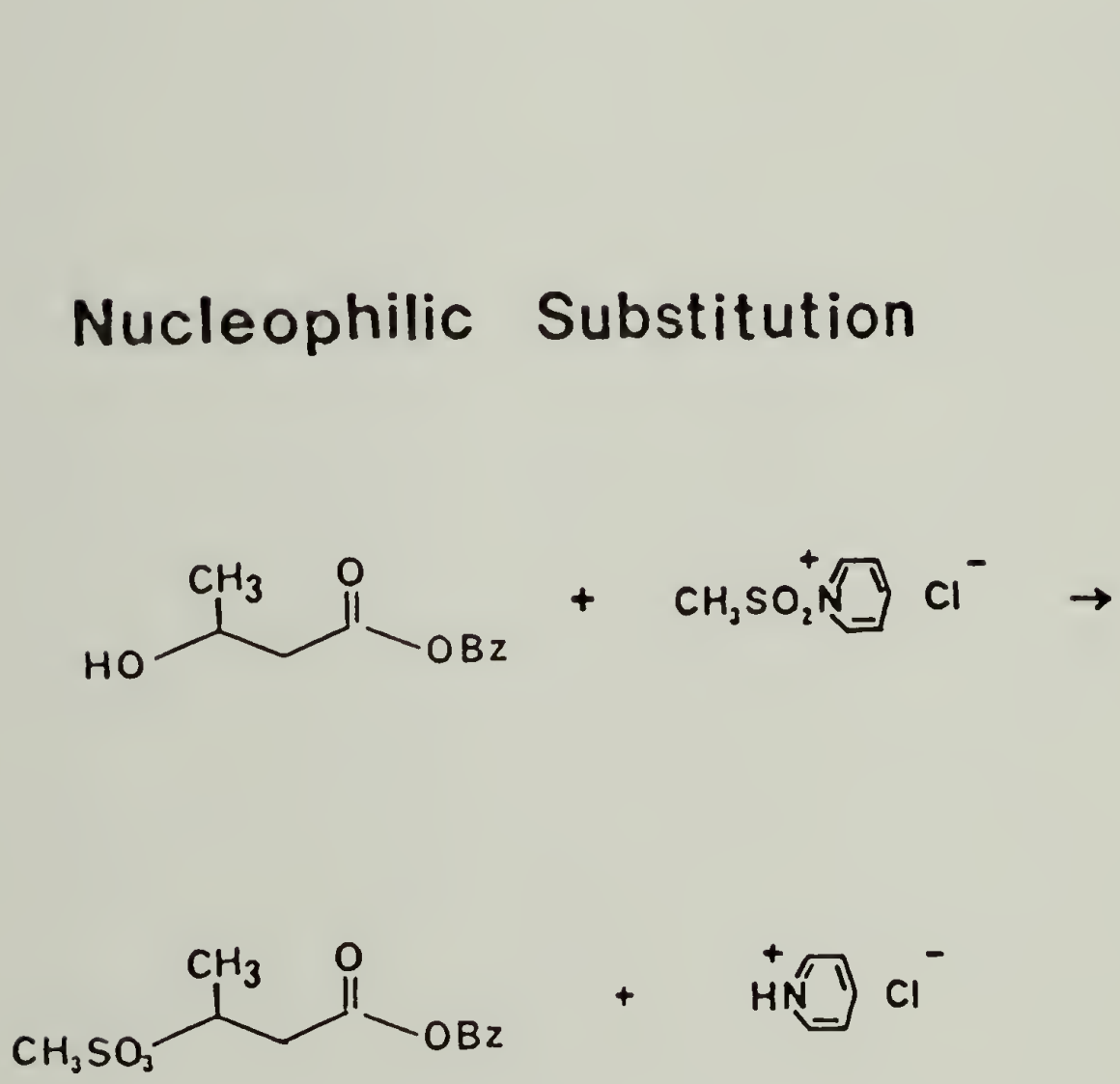


Figure 2.26 Preparation of benzyl [R]-O-mesylbutyrate.

under a nonhydrolytic condition.[58] The reaction occurred readily in a twofold excess of hydrobromic acid, without any side effects. The product IV was then separated from benzyl bromide by flash chromatography, which avoided decomposition of the product from high temperature fractional distillation. According to the polar-polar principle, chloroform and subsequently a chloroform/methanol (80:20) mixture were used as eluent solvents, and the acid product was collected after removing benzyl bromide. The separation procedure was monitored by thin layer chromatography (TLC) using an ultraviolet lamp (for the benzyl group) and the indicator bromocresol (for the mesyl group). A 70 percent yield of the purified [R]-O-mesylbutyric acid was obtained after the flash chromatography was twice performed. The phenyl absorption at 600-700 nm disappeared after the reaction with hydrobromic acid, indicating a complete removal of the benzyl ester group.

The catalytic hydrogenolysis of benzyl [R]-O-mesylbutyrate by palladium on active carbon was not used since the palladium catalyst would be poisoned or deactivated before a complete conversion.[32,59]

As mentioned previously, the neutralized mesylbutyrate solution was purified by extraction using cold ether to remove the unneutralized organic compounds before the lactonization. As shown in Figure 2.27, [R]-O-mesylbutyrate undergoes an internal S_N2 reaction, and the ß-lactone is transferred into the organic layer before it decomposes. It is worth noting that both

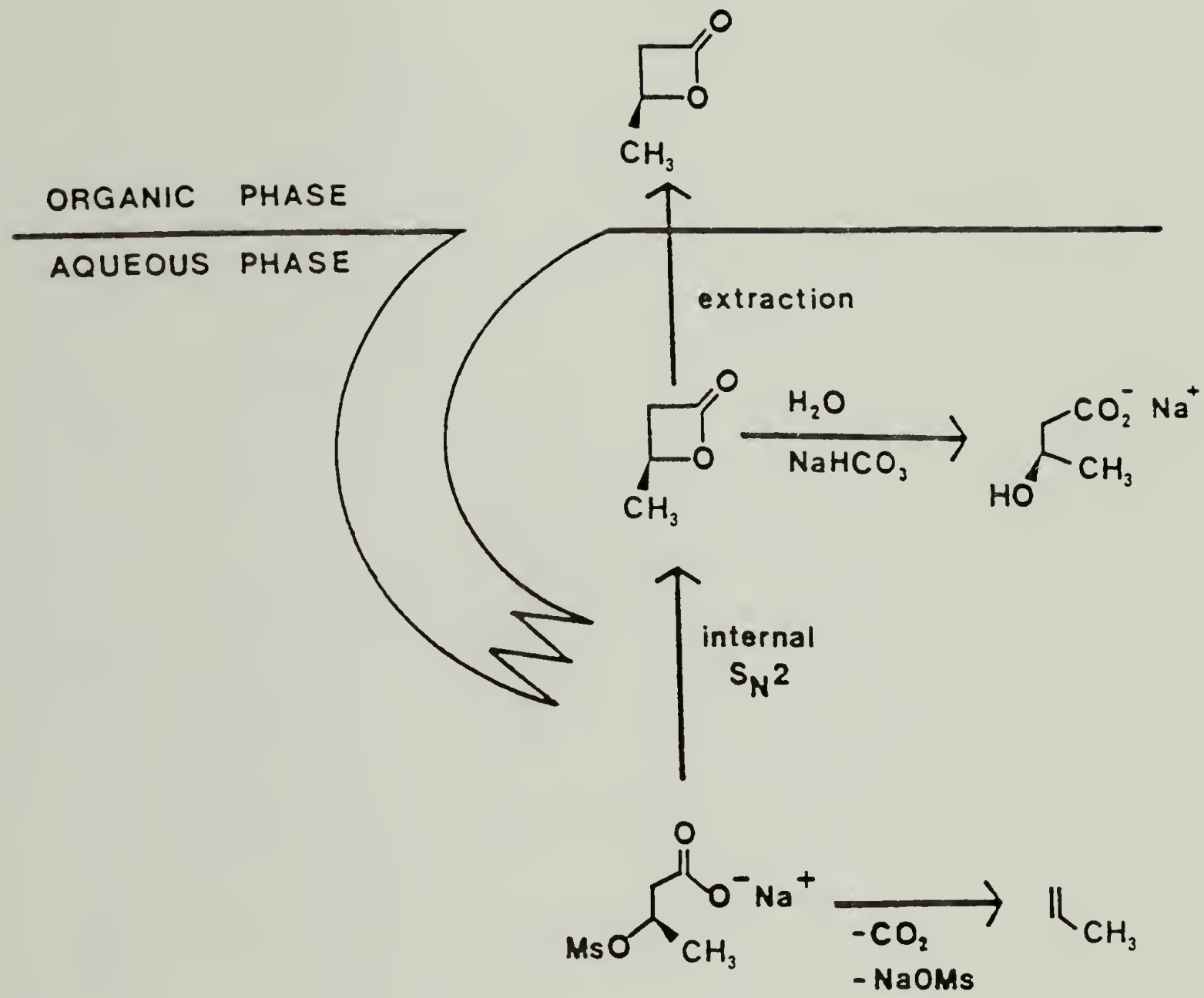


Figure 2.27 Lactonization of β-O-mesyl [R]-butyric acid to form [S]-butyrolactone.

the temperature control of not more than 35°C and the lactone isolation in every two hours during the reaction improved the yield greatly by limiting the side reactions. This two phase reaction system yielded a relatively pure ß-lactone because most of the impurities remained in the aqueous solution.

The mechanism that forms ß-BL from the ring closure of ß-mesylbutyric acid is a simple internal S_N2 reaction with an inversion of configuration at the ß-carbon.[53,60] Agostini and co-workers[61] found that 18% racemization had occurred in the preparation of ß-BL from an optically active ß-bromobutyric acid. They suggested that an attack of the bromide ion, which is liberated from an already formed lactone, on [S]-bromosuccinic acid produces [R]-bromosuccinic acid by an S_N2 type reaction. In our synthetic scheme of Figure 2.25, it is the first time one has used the mesylate as a leaving group to synthesize the optically active ß-BL, without complication of racemization.

2.2.2 Optical Purity of the [S]-ß-BL

Chiral shift regent, being composed of a paramagnetic cation and a chiral chelating ligand, has been used to determine the optical purity of a chiral compound by ^{1}H-NMR spectroscopy.[32,62] The chiral chelating ligand is necessary to distinguish and stabilize coordination enantiomers. The paramagnetic cation changes the local magnetic field around a binding site and, thereby, changes the chemical shift of the nuclei around the binding site.[63] As shown in Figure 2.28, the [R] and [S]-butyrolactones form two

diastereomeric coordination compounds with the chiral eropium shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium, $Eu(hfc)_3$.[64] The two enantiomers interact differently with the chiral shift reagent and, therefore, cause differences in the chemical shifts. Since the equilibrium between a shift reagent and an optical compound is fast on NMR time scale, the observed NMR spectrum is an average result of both the complexed and uncomplexed enantiomers of ß-BL.

The optical purity of [S]-BL obtained in this study was determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.[65] Figure 2.29 shows the ^1H NMR spectrum of [S]-BL with a sharp doublet at 1.9 (ppm) for the methyl protons (d) which can be used typically to determine its optical purity. In Figure 2.30, the ^1H-NMR spectra of both [S]-BL and [R,S]-BL are shown along with their expansions of the methyl protons (d) in the presence of 30 mol% $Eu(hfc)_3$. As expected, racemic ß-BL contains two doublets, in which the higher field doublet was assigned to the d-hydrogen of [R] enantiomer by the analysis of a mixture of BL stereoisomers.[66] Under the same conditions, the [S]-BL gave only the lower field doublet without further splitting. From this analysis, it was determined that the [S]-BL so prepared had an optical purity in excess of 97%.[67] That indicates that the synthetic strategy for creating [S]-BL, shown in Figure 2.25, works well without racemization. The high optical purity of [S]-BL was essential for the unambiguous interpretation of the stereochemical study[47] carried out in this study.

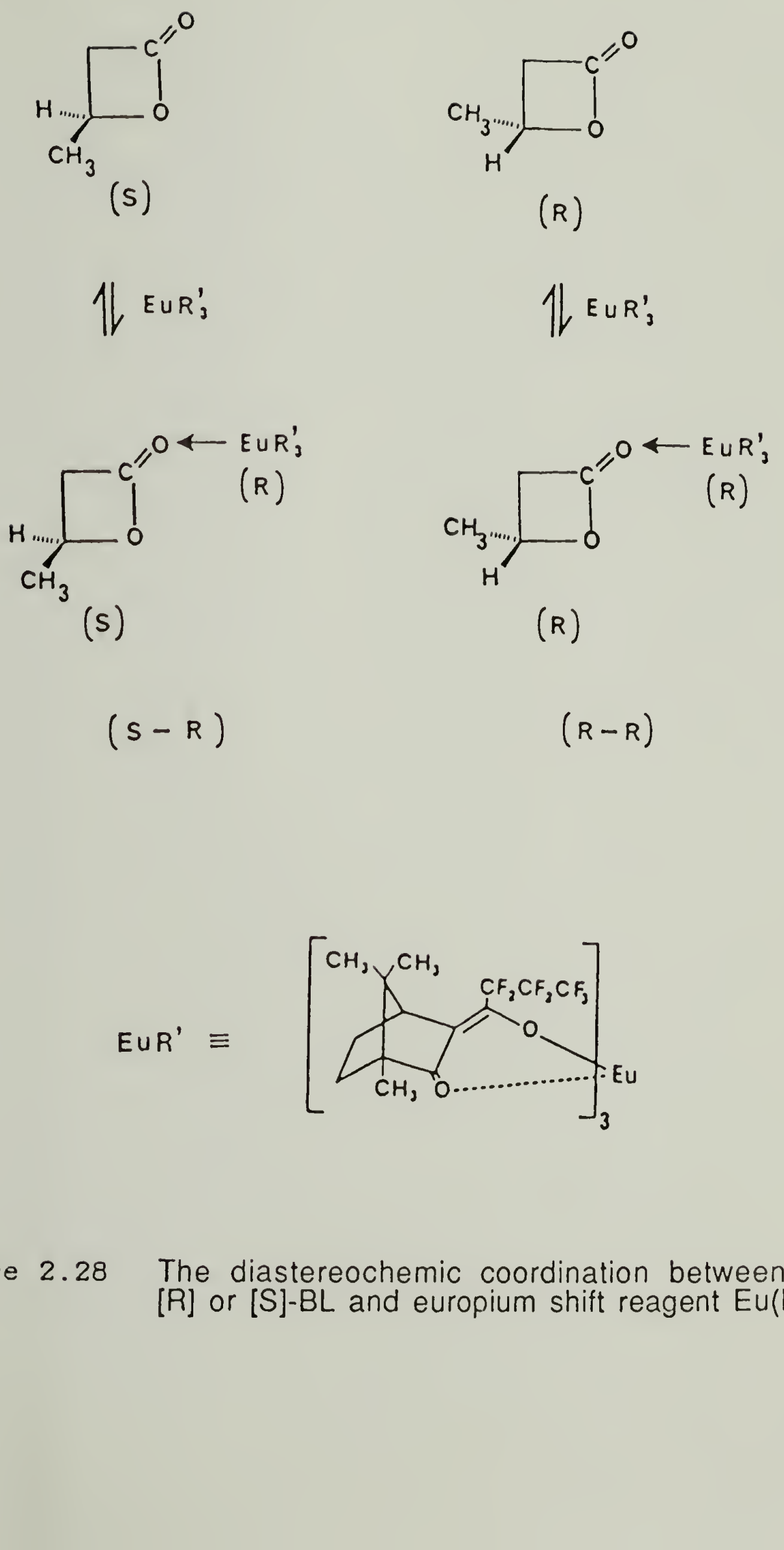


Figure 2.28 The diastereochemic coordination between [R] or [S]-BL and europium shift reagent $Eu(hfc)_3$

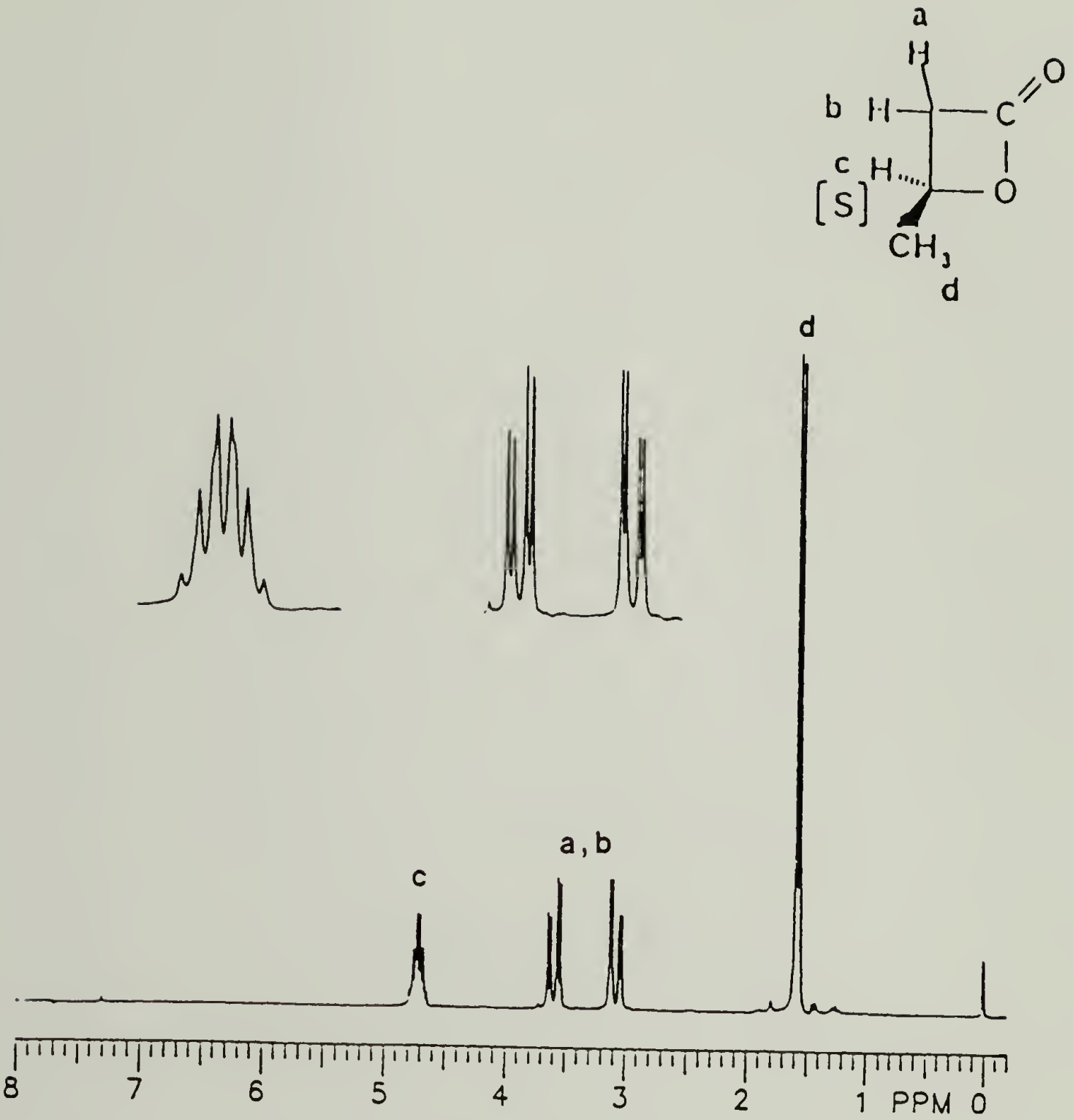


Figure 2.29 ^{1}H NMR spectrum of [S]-BL recorded in $CDCl_3$.

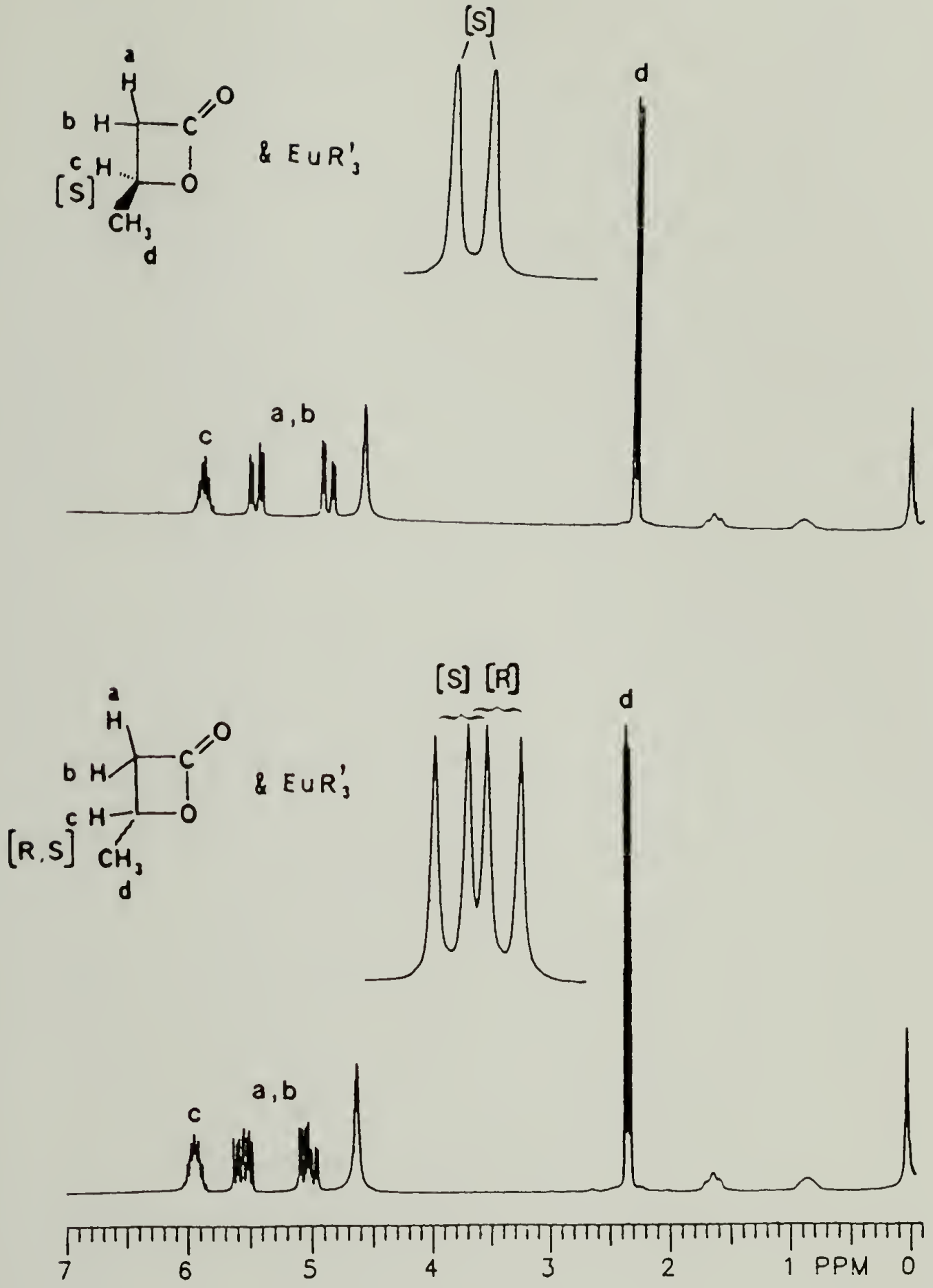


Figure 2.30 ^{1}H NMR spectra of [S] and [R,S]-BL along with expansions for the methyl region in presence of 30 mol% Eu(hfc)$_3$, recorded at 25°C in CCl_4/d_6-benzene (90/10).

2.2.3 Synthesis of the Optically Active Polymers from [S]-ß-BL

The synthesis of optically active polymers can be performed either by using a chiral catalyst or by starting from an isomeric monomer.[48,68-70] Le Borgne and coworkers studied the stereoselective polymerization of racemic BL with a chiral Zn-based catalyst, $ZnEt_2$/R-(-)-3,3-dimethyl-1,2-butanediol, Zn/[R]-(-)-DMBD.[45,69] They found the unreacted monomer was enriched in the [S] enantiomer and that the polymer obtained had the repeating units which were predominantly of [R] chirality. Therefore, it was concluded by Le Borgne and coworkers that the ring-opening polymerization with the Zn/[R]-(-)-DMBD catalyst proceeded primarily with retention of configuration.[69]

In our study, [S]-BL with high optical purity was used as a stereochemical probe to determine the mode for ring-opening polymerization with different catalysts. As shown in Figure 2.31, the ring-opening reaction of BL may proceed by bond breaking either between the carbonyl carbon and oxygen atom of the ß-lactone ring (path "a") with retention of configuration or between the ß-carbon and oxygen atom (path "b"), which could lead to either inversion of configuration or racemization.[71] Then, the P([R]-HB) and P([S]-HB) as well as P([R,S]-HB) may be produced as the results.

The catalysts investigated in this stereochemistry study are basically the same as those used in the racemic-BL polymerization. They are the "*In-situ*" $AlEt_3/H_2O$ (1:1), ethylaluminoxane EAO, $[-AlEt-O-]_n$, and $ZnEt_2/H_2O$ (1:0.6).

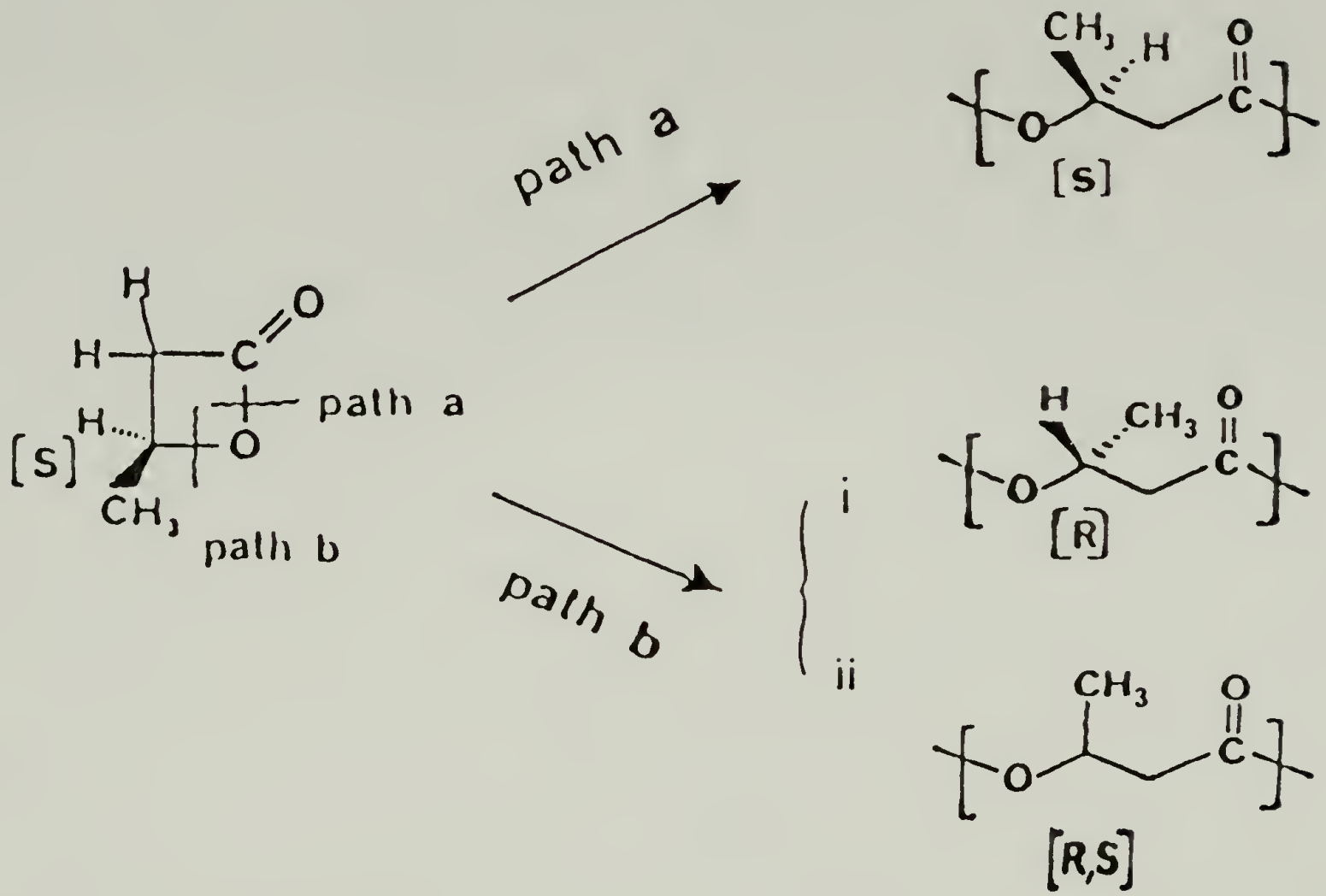


Figure 2.31 The stereochemistry of the ring-opening polymerization of [S]-BL.

2.2.3.1 Characterization of the Synthetic Optical Polymers

The results of the ring opening polymerization of [S]-BL with the above catalysts are summarized in Table 2.9. Comparing these results with the racemic-BL polymerization under the same conditions, the products synthesized from [S]-BL are crystalline powders with a values of ΔH_m between 20 to 22 cal/g. The high stereoregularity of these polymers was also shown in their ^{13}C NMR spectra, as shown in Figure 2.32 and 2.33, where only the isotactic signals were observed. The yields of polymerization using the "*In-situ*" $AlEt_3/H_2O$ and EAO catalysts, after AcAc treatment, were 30% and 50%, respectively. These values were higher than the corresponding yields of 15% and 20% in the racemic-BL polymerizations. The specific configuration of these synthetic polymers were then measured in their optical rotations by polarimeter.

It is very interesting to note, from Table 2.9, that the two stereoisomers of PHB, P([S]-HB) and P([R]-HB), were synthesized with the different catalysts.

The specific rotation of -7.0° for the polymer synthesized with the $ZnEt_2/H_2O$ (1:0.6) catalyst was in a similar magnitude but in an opposite direction from that of +7.4° for the natural origin P([R]-HB).[72] Thus, the polymerization must proceeded via path "a" (see Figure 2.31), with retention of the configuration to produce P([S]-HB).

When using the "*In-situ*" catalyst, the polymer produced had a specific rotation of +6.9° which is close to that of natural

Table 2.9 Synthetsis and characterization of the PHB stereoisomers from [S]-ß-BL

(a) Results of the polymerization

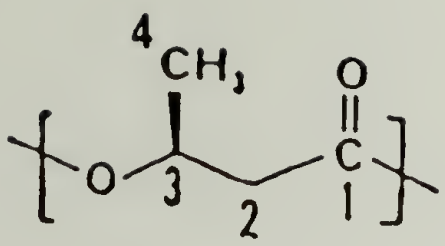
Sample	Catalyst	Yield (%)	$\bar{M}_w$ [a]	$\bar{M}_w/\bar{M}_n$ [b]
36	$ZnEt_2/H_2O$ (1/0.6)	72	20,000	1.5
37	*In-Situ* $AlEt_3/H_2O$ (1/1)	30	240,000	8.0
38	EAO[c] $[-AlEt-O-]_n$	50	190,000	7.8

a,b Determined by GPC, in chloroform, at 25°C.
c EAO is ethylaluminoxane.

(b) Stereo-activities of the optically active PHB's

Catalyst	Configuration of BL	%[R]/%[S][b] in PHB	$[a]^{30°c}$ (3.1, $CHCl_3$)
Alcaligenes eutrophus[a]	--	100/0	+7.4°
$ZnEt_2/H_2O$ (1/0.6)	[S]	0/100	-7.0°
In-Situ $AlEt_3/H_2O$ (1/1)	[S]	94/6	+6.9°
EAO $[-AlEt-O-]_n$	[S]	15/85	-5.8°

a Whole cell biocatalyst used for the commercial production of P([R]-HB).
b The polymer sample was obtained from Aldrich Chemical Co. Determined by ^1H NMR analysis in the presence of $Eu(hfc)_3$ for the degraded methyl hydroxybutyrates.
c Determined by polarimeter at 30°C and 365 nm, with ±0.4° error.



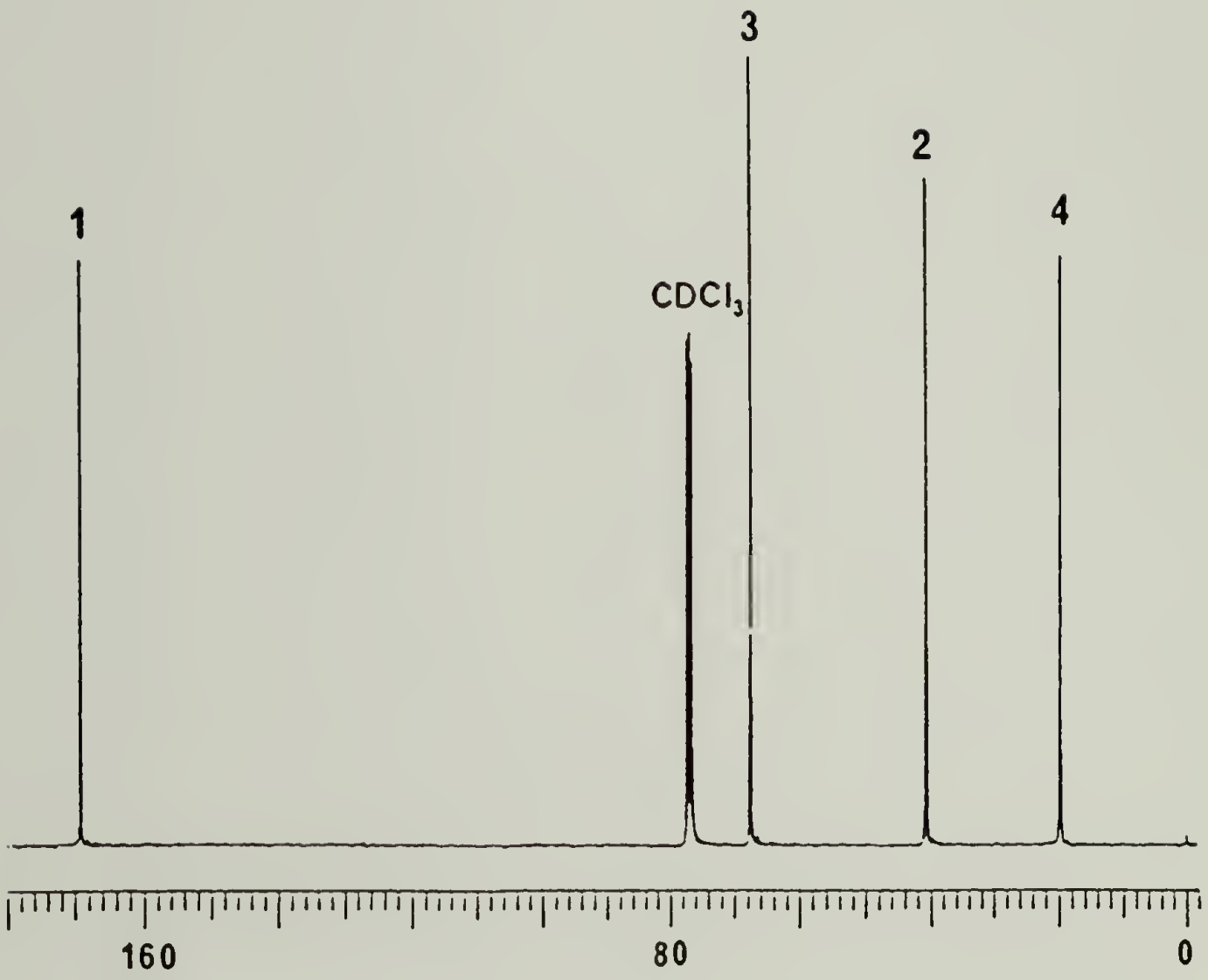
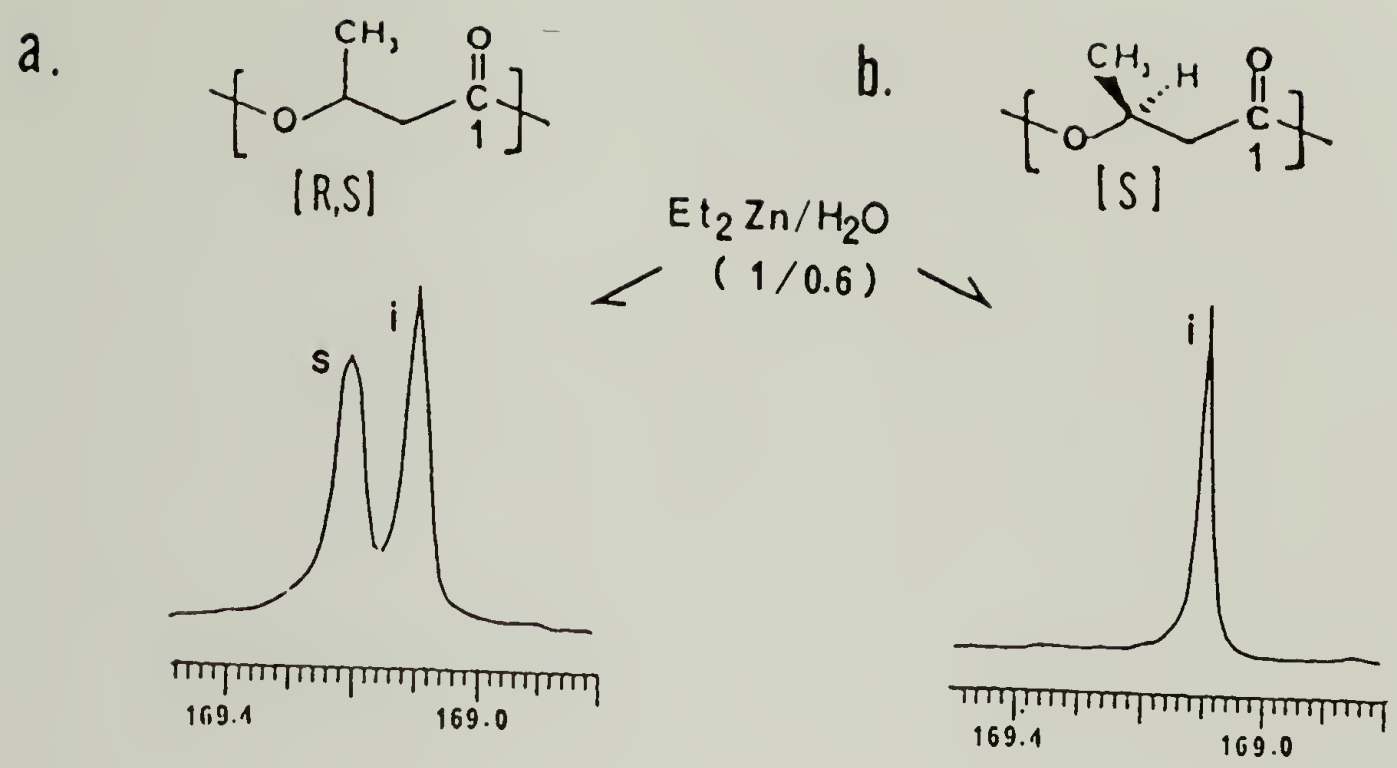


Figure 2.32 ^{13}C NMR spectrum of P([S]-HB) synthesized from [S]-BL using the Et_2Zn/H_2O catalyst.



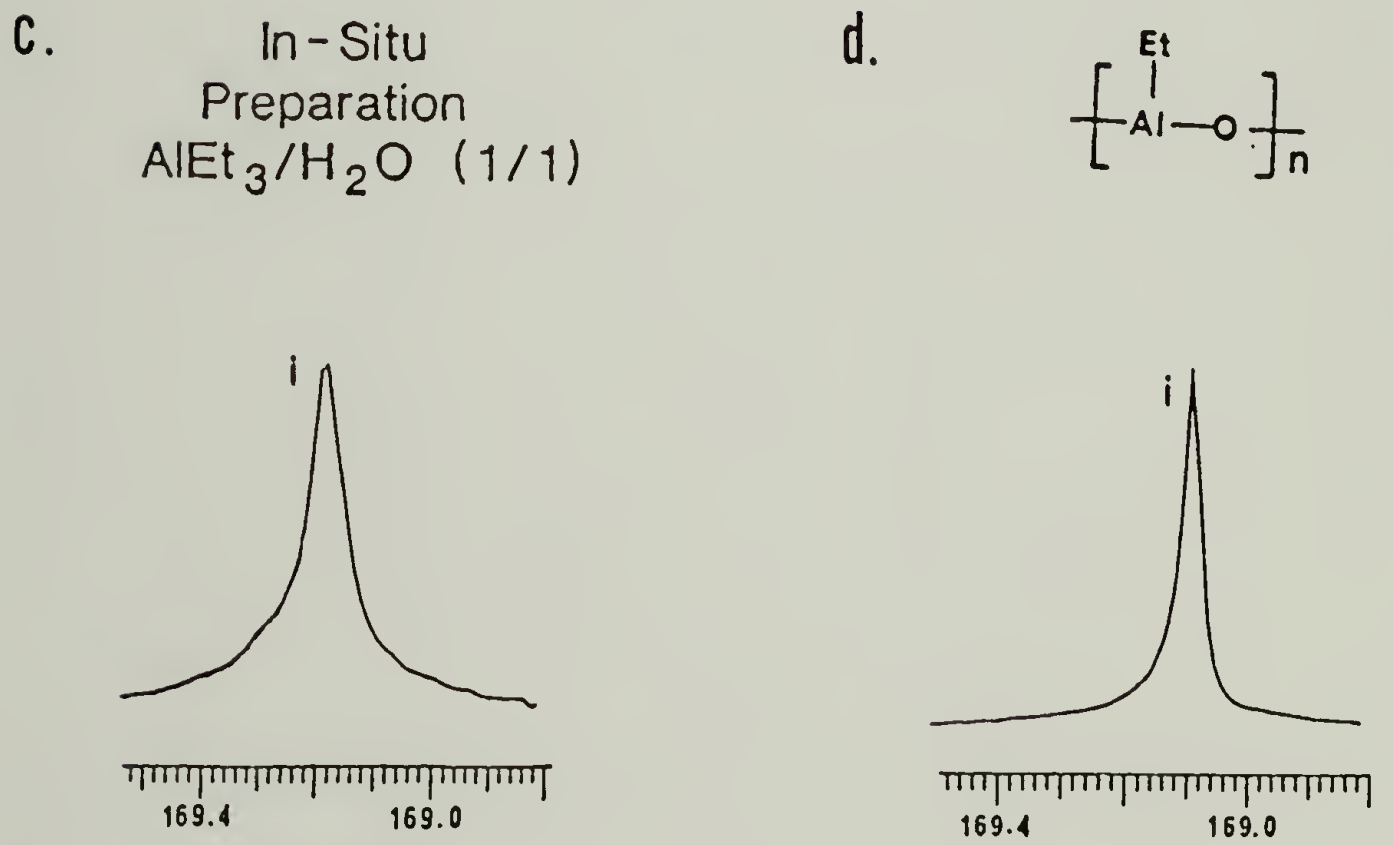


Figure 2.33 Expansions of the carbonyl carbon region from the ^{13}C NMR spectra of (a) the racemic and (b, c and d) optically active PHB synthesized using the different catalysts.

origin PHB of +7.4°. The reaction, thus, proceeded primarily via path "b" with an inversion of the configuration, producing a polymer which contained greater than 93% [R]-HB repeating units. This result seems to be in contradiction to the findings presented by Shelton and coworkers.[47-48] They reported that the ring-opening polymerization from one of the enantiomeric enriched BL was carried out by acyl-cleavage (path "a") in the $AlEt_3/H_2O$ (1:1) catalyst.

The different mechanisms of ring-opening observed for the $AlEt_3/H_2O$ system may result from the extreme sensitivity of the catalyst to the precise experimental conditions used in their preparations. In a previous study with ß-benzyl-malolactone (BML),[73] we prepared the catalyst by adding $AlEt_3$ in toluene (1.9 M) to the monomer at -78°C followed by the addition of H_2O ($AlEt_3/H_2O$, 1/1). From that procedure, a non-crystalline polymer was obtained in a 60% yield with an $\overline{M}_w$ of approximately 20,000 and an $\overline{M}_w/\overline{M}_n$ of less than 2.0. When the polymerization of BML was carried out under the same conditions as in the present study in which the catalyst was prepared firstly in the polymerization ampoule before the addition of monomers, the results were dramatically different. In this case, the polymer product was crystalline but was obtained in only a 12% yield, it had an $\overline{M}_w$ of approximately 400,000 and an $\overline{M}_w/\overline{M}_n$ about 8.0.[73] These results clearly show how sensitive the polymerization reaction is to the procedure used to prepare the $AlEt_3/H_2O$ catalyst.

Indeed, the polymerization of enantiomerically enriched BL by

Shelton and coworkers was carried out by preparing the catalyst in the presence of monomer,[47] while in the present study the "*In-situ*" $AlEt_3/H_2O$ was prepared before the addition of monomer.[73] The differences in the methods above undoubtedly account for the different modes of ring-opening observed. It is likely, therefore, that by careful alteration of the method used to prepare an $AlEt_3/H_2O$ catalyst the mode of the ring-opening reaction can be changed completely to achieve any desired stereochemistry in the polymer. This point is again illustrated from the results discussed below which describe the polymer stereochemistry obtained when the EAO catalyst was used to polymerization od ß-BL.

In this case, the polymerization of [S]-BL proceeded primarily via path "a" with retention of configuration (see Figure 2.31), although the magnitude of the specific rotation of the product was less than that of natural origin PHB (see Table 2.9). The P(HB) product synthesized with the EAO catalyst contained 85% [S] repeating units (see Table 2.9-b). The lower isotopic purity of the repeating units, relative to the starting monomer, was not due to racemization of the monomer before its polymerization. This was indicated by the ^{1}H-NMR spectrum, in the presence of $Eu(hfc)_3$, of the non-polymerized monomer recoved from the reaction mixture. The unreacted lactone had an optical purity in excess of 97% of the [S]-configuration.

2.2.3.2 Fractionation of the Optical Active Polymer

Because of the relatively lower specific rotation of the

Table 2.10 Fractionation of the optical active PHB synthesized with the catalyst EAO.

Fraction[a]	$\bar{M}_w$[b]	$\bar{M}_w/\bar{M}_n$[b]	Weight %[c]	$[a]^{30}$ (3.1, $CHCl_3$)
Unfract. sample	190,000	7.8	100	-5.8°
High MW	430,000	14.0	30	-3.6°
Middle MW	20,000	1.5	50	-7.2°
Low MW	8,000	1.3	20	-7.1°

a Fractionation was carried out by solubility differences.

b Determined by GPC, in chloroform, at 25°C.

c Relative to the unfractionated sample.

polymer obtained with the EAO catalyst (see Table 2.10), a further fractionation of this sample was undertaken by a cloudy-point experiment. This experiment was based on the differences in solubility.[74] The experiment was successful in separating the middle and low molecular weight fractions (in 70 wt.% of the whole sample) having a specific rotation equal in magnitude but opposite in sign to the value for natural origin P([R]-HB) (see Table 2.10). The result suggests that for the EAO catalyst there exist major active sites that produce relatively lower molecular weight chains by the ring-opening polymerization of BL via path "a" with little or no racemization.

The high molecular weight fraction was still bimodal in GPC and contained a relatively higher molecular weight polymer, which corresponds to the high molecular weigh GPC peak of the unfractionated polymer (see Figure 2.34). This fraction had a specific rotation with a much smaller value but of the same sign as the middle and low molecular weight fractions (see Table 2.10). This part of the polymer is a mixture or stereoblocks of P([S]-HB) and P([R]-HB). This mixture is less enriched in [S] enantiomer than it was before the fractionation.

The expanded carbonyl region of the ^{13}C NMR spectrum of the unfractionated P(HB) sample using the EAO catalyst is shown in Figure 2.33-d. From the single peak, corresponding to the isotactic signal, it is clear that the polymer produced from [S]-BL with the EAO catalyst did not contain measurable quantities of syndiotactic diads. The single isotactic peak in Figure 2.33-d in combination

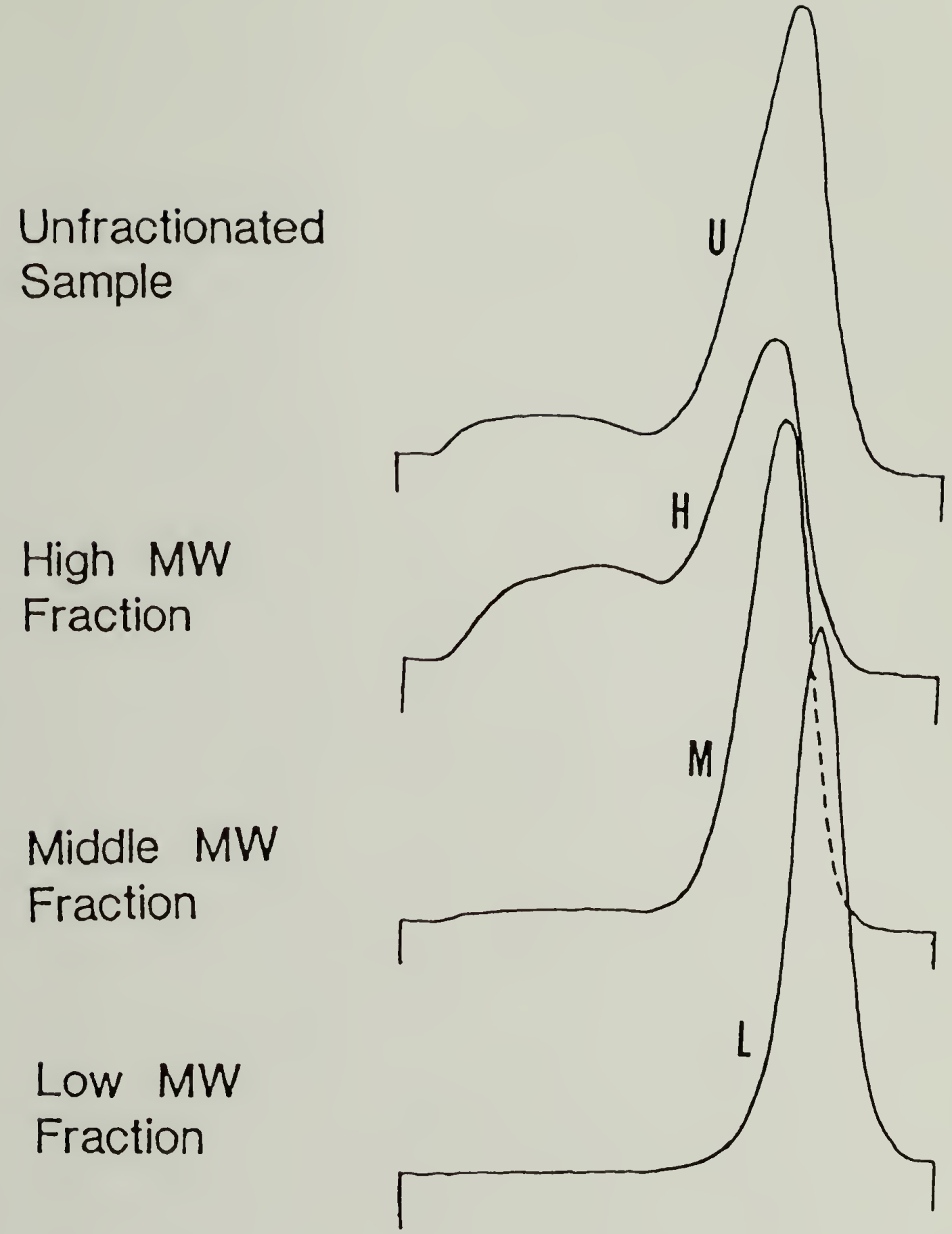


Figure 2.34 GPC chromatography of the PHB synthesized using the EAO catalyst and measured before and after fractionation.

with the specific rotations of the unfractionated polymer and the high molecular weight fraction suggest that either very long blocks or more likely whole chains contain only [R] units in the high molecular weight fraction along with a larger amount of polymer which contains exclusively [S]-repeating units.

It is interesting to compare the polymerization of [S]-BL to that of racemic BL's in the EAO catalyst system. In the latter case, a relatively high molecular weight and highly crystalline fraction (60-80% of whole AcAc treated sample) was obtained together with a lower molecular weight fraction which showed little crystallinity.[52,73] The results from both of the polymerizations suggest that the EAO catalyst has at least two very different types of active sites.[73] It would not be surprising, therefore, if these different active sites operated via different ring-opening mechanisms, although the major mode of the ring opening apparently proceeds via path "a" with a retention of configuration. Similarly, Krichedorf and coworkers found that aluminum triisopropoxide is also capable of polymerizing BL via path "a".[57]

In summary, the stereochemical course for the ring-opening polymerization of BL can be controlled by choosing a proper catalyst system. The synthetic analogues of bacterial PHB, therefore, can be obtained with the desired stereochemistry.

2.2.4 Polymerization of [S]-ß-BL with $Et_2AlOAlEt_2$

The complication of the ring-opening mechanism in the

oligomeric EAO system raises a question concerning the structure of the catalyst. For the EAO compound prepared by a high temperature and high vacuum treatment in this study, the linear oligomer, $-(AlEtO)_n-$, is expected to be the predominant structure because of disproportionation,[13-14] but the existence of a small fraction of $Et_2AlOAlEt_2$ can not be excluded. As discussed in the previous paragraph, at least two different active centers were present in the EAO catalyst system. The small oligomers, such as a dimer, $Et_2AlOAlEt_2$, or a trimer may catalyze the reaction differently and, therefore, form the polymers with different tacticities.[11-14]

In order to elucidate the catalyst behavior of the $Et_2AlOAlEt_2$ and $-(AlEtO)_n-$, a synthesis of the pure catalyst $Et_2AlOAlEt_2$, and the polymerization of [S]-BL with this catalyst was carried out.

The catalyst was prepared by reacting Et_2AlOLi and Et_2AlCl in 1:1 ratio.[75-76] The product should contain only a dimer and no other oligomers, which may exist in the EAO catalyst. According to the literature, this dimer, $Et_2AlOAlEt_2$, may produce a PHB of different stereoregularity from that of the oligomer catalyst, $-(AlEtO)_n-$.

The polymer formed by the catalyst $Et_2AlOAlEt_2$ had a specific rotation of +1.6°, it is, therefore, either a mixture of two stereoisomers enriched in a small amount of P([R]-HB), or a partially racemilized product. Comparing the characteristics of the polymers resulting from the catalysts EAO and $Et_2AlOAlEt_2$, it was found that the polymer synthesized with the dimer was lower

in yield, molecular weight, melting point and value of ΔH_m. This indicates that the existence of the dimer could decrease the activity of the EAO catalyst and therefore cause a decreased stereoregularity in the polymer, although a definite mechanism of $Et_2AlOAlEt_2$ on the ring-opening polymerization was not clear yet. An adverse effect of $Et_2AlOAlEt_2$ revealed in the stereoregular polymerization of ß-lactone has been discovered in the stereospecific polymerization of propylene oxide.[14]

2.2.5 Stereoisomeric Purity of the Synthetic PHB

The stereoisomeric purities of the repeating units of each of the polymers were determined by an acid catalyzed methanolysis of the polymers to form the constituent methyl ß-hydroxybutyrate stereoisomers. No racemization occurs during the following reaction.[54]

$$\text{P([R]-HB) or P([S]-HB)} \xrightarrow[\text{MeOH}]{3\%\ H_2SO_4} \text{[R]-methyl hydroxybutyrate ([R]-MHB) or ([S]-MHB)}$$

The ^1H NMR spectrum of the MHB degraded from the polymer synthesized with the $ZnEt_2/H_2O$ catalyst is shown in Figure 2.35, in the presence of 20 mol% $Eu(hfc)_3$. Expansions of the peaks for the hydrogen atoms in the methoxy group, which are designated as d, are displayed in Figure 2.36.

In Figure 2.36-a, an expansion is shown of the d hydrogen signal from the spectrum of methyl [R,S]-ß-hydroxybutyrate, which

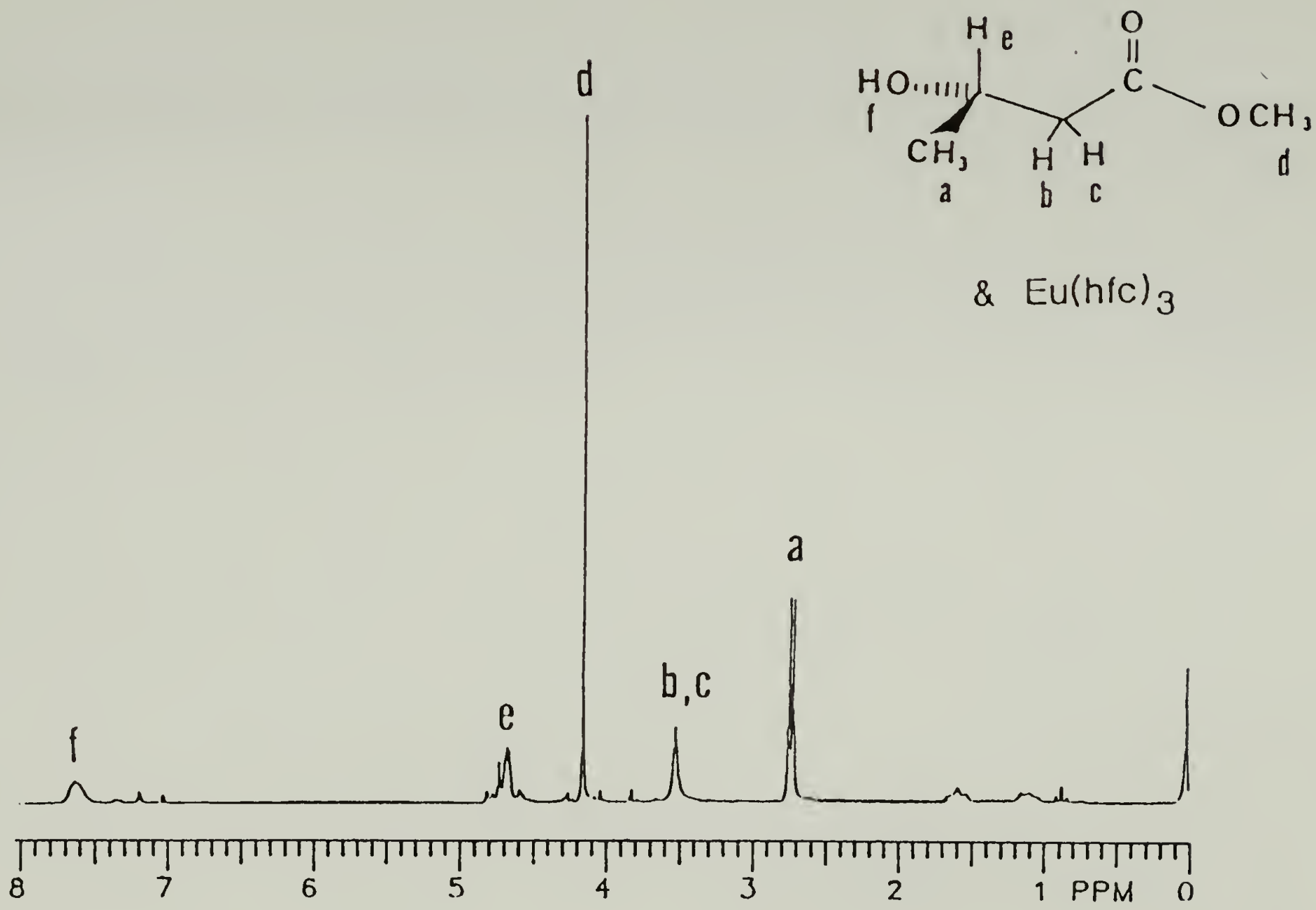


Figure 2.35 ^1H NMR spectrum of [S]-methyl hydroxylbutyrate (MHB) (obtained by the methanolysis of the P([S]-HB) synthesized using the Et_2Zn/H_2O catalyst) complexed with 20 mol% Eu(hfc)$_3$.

was obtained from the methanolysis of a [R,S]-P(HB) and complexed with the shift regent. The upfield peak was assigned to the [R] stereoisomer from an isomeric mixing experiment.[80] The expansion of the MHB obtained from methanolysis of the P([S]-HB), which was in turn obtained from [S]-BL with the $ZnEt_2/H_2O$ catalyst, shows a single peak for the d hydrogen, in Figure 2.36-b, which corresponds to the [S] isomer of MHB. This result in combination with the specific rotation for the synthetic polymer, shown in Table 2.9, indicated that the ring-opening polymerization of [S]-BL with the $ZnEt_2/H_2O$ catalyst must proceed exclusively along path "a", forming a stereoisomer P([S]-HB) in high optical purity.

The polymers synthesized with both the "*In-situ* " $AlEt_3/H_2O$ (1:1) and EAO catalysts, especially the latter one, show lower stereoisomeric purities in their related methyl esters in Figure 2.36-c and d, respectively. From spectrometer integration of Figure 2.36-c, a stereoisomeric mixture of 95% [R] and 5% [S] was obtained.[77] The small shoulder in signal [R] is probably due to impurities in the sample. The small amount of [S] unit existed in the P([R]-HB) may be the reason for the slightly decreased value of the specific rotation for the sample (see Table 2.9). It was not surprising that a P(HB) mixture of 85% [S] and 15% [R] was observed from the curve fitting of Figure 2.36-d, considering the relatively lower specific rotation of the sample obtained with the EAO catalyst, as mentioned previously. It is interesting to compare the similarity of this integration result with that of the GPC bimodal

distribution of the unfractionated P(HB) sample shown in Figure 2.34, from which a ratio of 84/16 (low/high molecular weight) was obtained. It is likely, therefore, that each peak of the molecular weight contains only one of the stereoisomers.

In summary, it is a useful method for employing the related methyl esters obtained from the methanolysis to determine the stereoisomeric purity of the synthetic polymers. Both ^{1}H NMR spectroscopy and specific rotation show a positive result in producing the optical pure polymers, while the former method gives both qualitative and quantitative analysis.

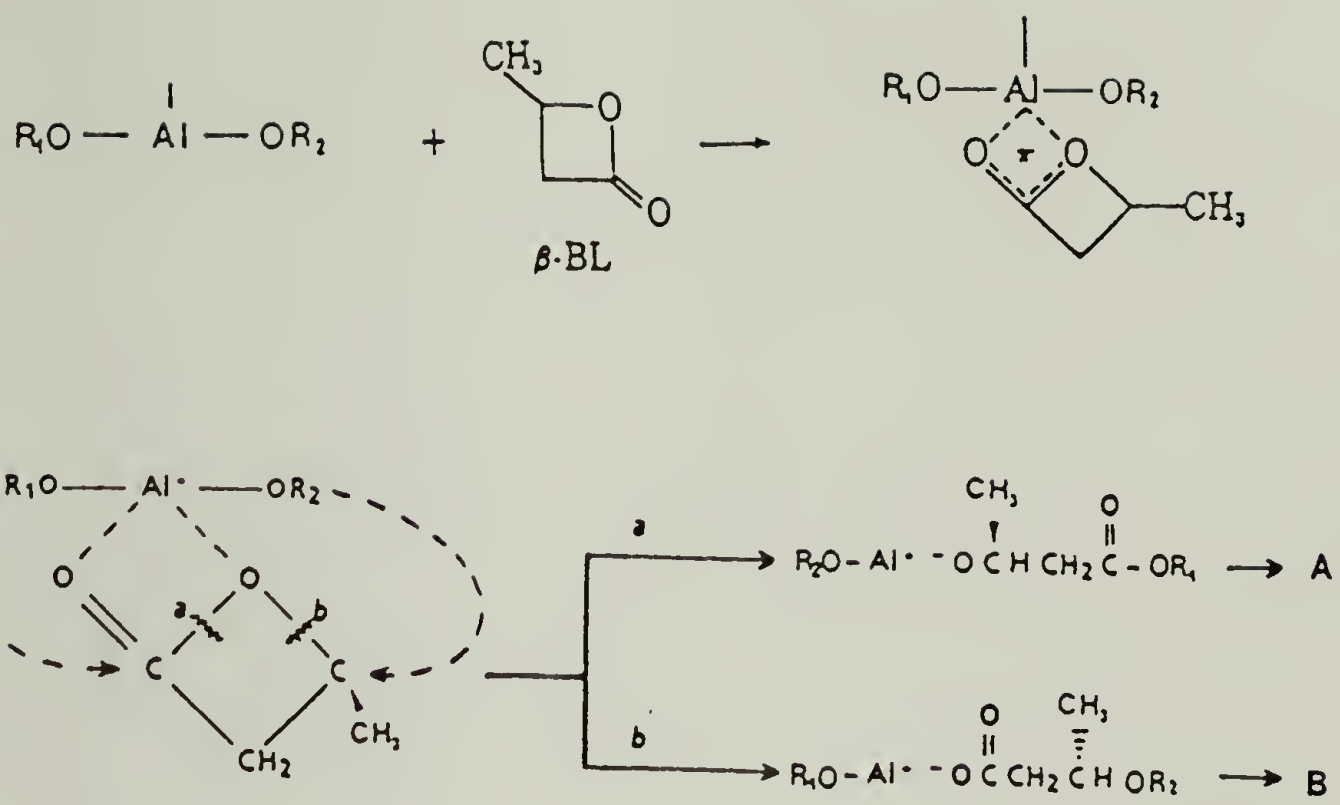
2.2.6 Mechanism of the Ring-Opening Polymerization

In spite of the usefulness of the AlR_3/H_2O and $ZnEt_2/H_2O$ catalysts for the ring-opening polymerization of ß-lactones, the exact nature of these catalysts has been open to question.[78-79] A special investigation by Tani and coworkers was carried out on interactions between the Al or Zn-catalyst and ß-isopropyl-propiolactone in 1:1 ratio.[14] The result, determined by chemical shifts of the corresponding compounds in ^{1}H and ^{13}C NMR spectra, revealed that coordination was observed only between the AlR_3/H_2O catalyst and lactone. This difference in coordination ability of the lactone toward the Al and Zn catalysts can be used to interpret the difference in stereo-controlling of the lactone polymerization by the two catalysts. Since both the Al and Zn catalysts have been suggested as being cationic in nature,[13,14] the

differences in electrophilic properties, and therefore, the differences in oxygen-philicity of the Al and Zn atoms seem to be responsible for the coordination ability and site-selectivity in the ring opening reaction. The stronger coordination ability of the Al-catalyst to lactone makes the ring-opening reaction more stereo-selective, so the polymer produced has a higher stereoregularity. In combination with the results obtained from the mechanistic study described previously, the different modals for the ring-opening propagation reaction between the Al or Zn-catalyst and ß-monosubstituted ß-propiolactone are proposed in Figures 2.37-a and b, respectively.

In Figure 2.37-a, it was suggested that the mechanism of polymerization involves a coordination between the lactone and aluminum, followed by ring opening reaction and insertion of the monomer unit into the Al-O bond, which is reported to be an active center for this kind of catalyst.[14,80] The behavior of the Al-catalyst in this model is like a *coordinated anionic* initiator.[81,82] With this mechanism, ring opening polymerization of ß-monosubstituted ß-propiolactone can be carried out through either path "a" or path "b", leading to two types of coordinated anionic chain ends for the propagation reaction. That occurred in the ring-opening polymerizations of [S]-BL with the EAO and the *"In-situ"* catalysts, by path "a" and path "b", respectively.[83] Considering the stereo-effect of the chain-end or the last monomer unit, the mechanism of the coordinated polymerization may be represented as below:

a.



b.

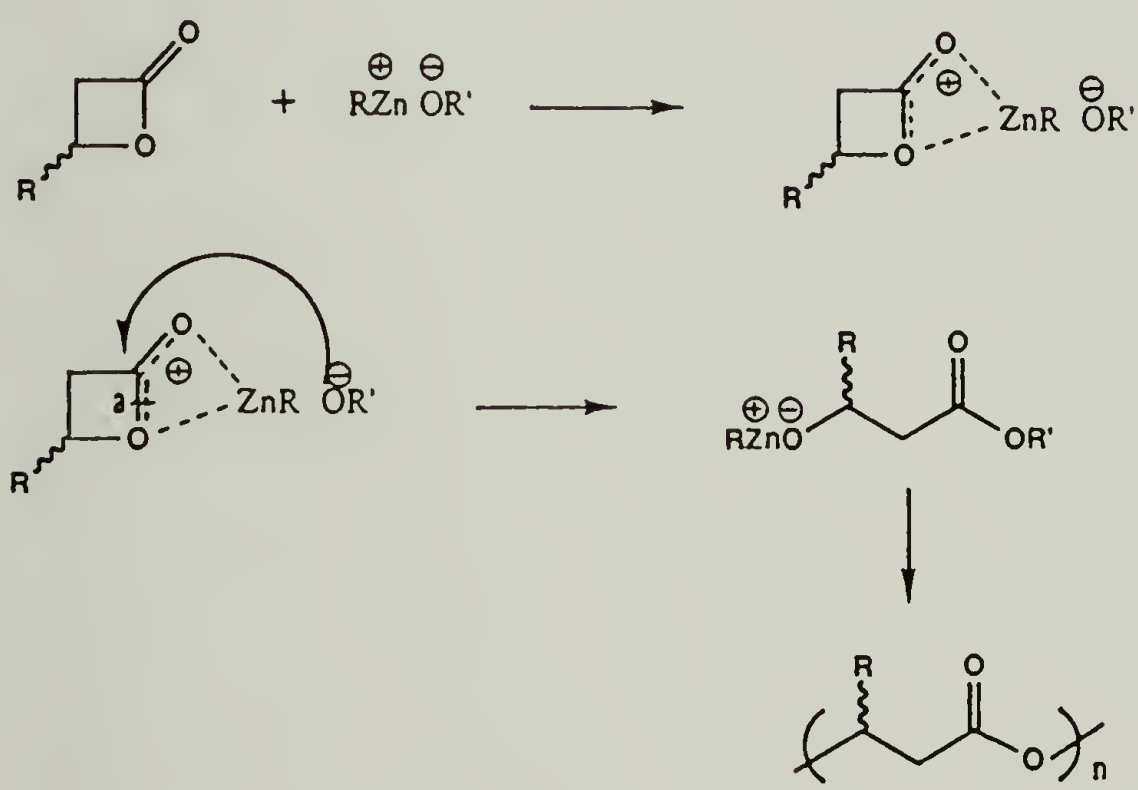
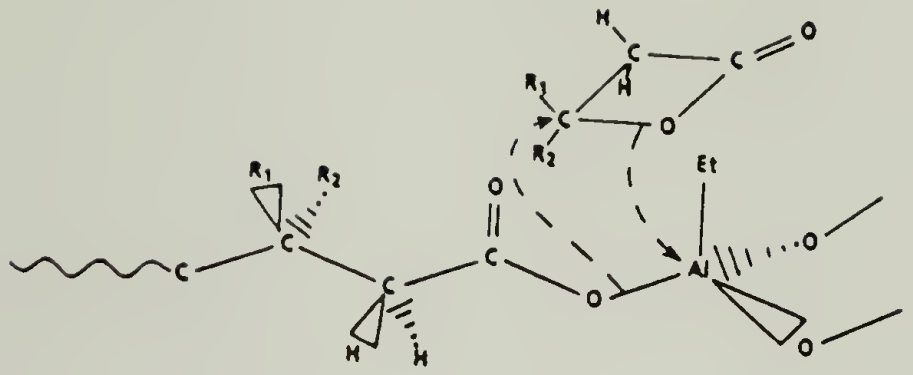


Figure 2.37 The ring-opening mechanism study using the catalysts Al- and Zn-water.



Whether the aluminum-oxygen bond is more ionic or covalent in character is not clearly known yet.

The $ZnEt_2/H_2O$ catalyst, which is more cationic in character,[29] seems to promote the polymerization by a different mechanism, as shown in Figure 2.37-b. The ring-opening reaction proceeds by an S_N1 mechanism through the attacking of the acyl-carbon with an alkyloxide group. The propagation reaction, then, will be continued in the same manner by insertion of the monomer unit into the Zn-O bond.

The reason for the nucleophilic attack on the acyl-carbon of the monomer is probably because the positive charge is more concentrated on the acyl-carbon after the formation of a complex structure between the Zn-catalyst and lactone. This mechanism has been proven by the production of optically pure P([S]-HB) from [S]-BL, where no configuration inversion or racemization occurred.

It should be noted that the $ZnEt_2/H_2O$ (1:0.6) catalyst is different from the typical cationic catalyst e.g., BF_3-OEt_2 and $SnCl_4$, which usually causes a chain transfer or a termination at a very early stage.[13,14,29]

It is clear, that coordination between the catalyst and monomer is the key point for the stereo-controlling of the ring-opening polymerization wether the reaction proceeds through path "a" or path "b".

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CHAPTER 3
EXPERIMENTAL

3.1 Reagent and Solvents

The following reagents were purchased from Aldrich Chemical Co. and used without purification: Natural origin polyhydroxybutyrate (P([R]-HB), $\bar{M}_n$=150,000), bromosuccinic acid (96%), acetyl chloride (98%), toluenesulfonic acid (monohydrate, 99% purity), dry pyridine, anhydrous mesyl chloride, HBr (30-32 wt.% in glacial acetic acid), methylene chloride, Et_3Al (1.9 M in toluene), Et_2Zn (neat), 5,10,15,20-tetraphenylporphine ($TPPH_2$) and diethylaluminum chloride (Et_2AlCl). [R,S]-butyrolactone, obtained commercially by Aldrich Chemical Co., distilled twice over CaH_2 in an atmosphere of dry argon, and the fraction boiling at 70-72°C (30 mm Hg) was collected (purity: 99.5% by GC). Technical grade solvents were used in the polymer extractions. Spectrophotometric grade solvents were used in the monomer syntheses and the polymer characterizations. Benzyl alcohol, purchased from Fisher Chemical Alert., was refluxed over CaH_2 and distilled under argon before use.[1] Methanol was refluxed over Na° and distilled at 64°C under argon. Distilled water was used in the preparation of catalysts. Toluene was dried by refluxing over sodium-potassium alloy in an atmosphere of dry argon for 16 h and distilled before use.[1]

3.2 Monomer Preparations

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CHAPTER 3

EXPERIMENTAL

3.1 Reagent and Solvents

The following reagents were purchased from Aldrich Chemical Co. and used without purification: Natural origin polyhydroxybutyrate (P([R]-HB), Mn=150,000), bromosuccinic acid (96%), acetyl chloride (98%), toluenesulfonic acid (monohydrate, 99% purity), dry pyridine, anhydrous mesyl chloride, HBr (30-32 wt.% in glacial acetic acid), methylene chloride, Et_3Al (1.9 M in toluene), Et_2Zn (neat), 5,10,15,20-tetraphenylporphine ($TPPH_2$) and diethylaluminum chloride (Et_2AlCl). [R,S]-butyrolactone, obtained commercially by Aldrich Chemical Co., was distilled twice over CaH_2 in an atmosphere of dry argon, and the fraction boiling at 70-72°C (30 mm Hg) was collected (purity: 99.5% by GC). Technical grade solvents were used in the polymer extractions. Spectrophotometric grade solvents were used in the monomer syntheses and the polymer characterizations. Benzyl alcohol, purchased from Fisher Chemical Alert., was refluxed over CaH_2 and distilled under argon before use.[1] Methanol was refluxed over Na° and distilled at 64°C under argon. Distilled water was used in the catalyst preparations. Toluene was dried by refluxing over sodium-potassium alloy in an atmosphere of dry argon for 16 h and distilled before use.[1]

3.2 Monomer Preparations

3.2.1 Synthesis of Racemic Benzyl Malolactone[2]

a. Bromosuccinic Anhydride Bromosuccinic acid was placed in an one-neck flask equipped with a mechanical stirrer and condenser with an argon inlet and outlet. Acetyl chloride was added in 3:1 molar excess to the acid. The mixture was stirred and refluxed for 5 h, a yellowish homogeneous solution was obtained at the end. The by-products, acetyl acid and the anhydride as well as the extra acetyl chloride, were removed by vacuum distillation. The remaining dark brown residue was distilled twice, under vacuum (0.1-0.15 mm Hg) at 89-91°C, leaving a clear water-white oil, which crystallized to a white solid with a M.P. 32-34°C. The yield of bromosuccinc anhydride was 90-95%. Elemental Anal. Calcd. from $C_4H_3O_3Br$: C,26.84; H,1.69; O,26.82; Br,44.64. Found: C,26.92; H,1.72; O,26.66; Br,44.70. IR spectrum #1 (App.A).

b. Benzyl Bromosuccinate(s) Purified benzyl alcohol was added dropwise into bromosuccinic anhydride in a 1:1 molar ratio under an argon atmosphere. Above procedure was performed slowly and with stirring because the reaction was exothermic. The reaction system was heated to 60°C and maintained at that temperature until no absorption peaks of alcohol and anhydride could be detected by IR spectroscopy. The benzyl bromosuccinate obtained was a mixture[3] of two kinds of esters in a 70:30 molar ratio (described in 2.1.1). The spectra of this mixture: IR #2 (App.A) and ^{1}H-NMR #1 (App.B).

c. Benzyl Malolactonate The above mixture (66 grams, 0.23 moles) was placed in an one liter beaker with 550 mL of water. Sodium bicarbonate (26 grams) was added slowly, with stirring, to form a homogeneous aqueous solution with a final pH of 7-8. The solution was extracted twice with cold ether to remove unneutralized organic compounds. The neutralized aqueous solution was placed in a two liter, three-neck flask containing 550 mL benzene and equipped with a mechanical stirrer and a condenser. The solution was gentally heated to 40-45°C and vigorously stirred for 4 h (such that the two phases mixed to appear as one milky-white phase), then, it was poured into a two liter separate funnel. The aqueous phase (lower one) was removed and discarded. The organic phase was washed each twice with 250 mL of a 5% (w/v) solution of sodium bicarbonate and 250 ml of distilled water. After drying with anhydrous magnesium sulfate, the solution was suction filtered, and benzene was evaporated under vacuum, giving an oily product. This residue was dissolved in 300 mL of diethyl ether and then washed and dried again, as described above, to produce 30 grams (0.15 moles) of benzyl malolactone with a 90% yield. The crude lactone was purified by two vacuum distillation (≤10 mm Hg) over CaH_2 using a short-path still at 85-100°C. The monomer was used immediately after the 2nd distillation. Elemental Anal. Calcd. for $C_{11}H_{10}O_4$: C,64.07; H,4.89; O,31.04. Found: C,63.77; H,5.54; O,31.70. IR spectrum #3, ^{1}H-NMR #2 and ^{13}C-NMR #1.

3.2.2 Synthesis of Optically Active [S]-Butyrolactone

a. [R]-Methyl-ß-Hydroxybutyrate[4,5] 80 grams of P([R]-HB) (0.93 mol) was dissolved in 400 mL methylene chloride in a 2 liter single-neck flask. 388 mL of methanol (9.59 mol), acidified with 3% (v/v) H_2SO_4, was added under argon. The solution was, then, refluxed in a 80-85°C external oil bath for 26 h. The above system was diluted with 200 mL ether and extracted with 150 mL half saturated NaCl solution in a 2 liter separator funnel. The organic phase was washed three times with 200 mL of saturated $NaHCO_3$ solution, once with 150 mL of saturated aqueous NaCl and, then, dried over $MgSO_4$. After the solvents being removed, the product was distillated under reduced pressure (100 mm Hg) at 75°C, through a vigrues column and a short path distillation apparatus. The crude product was further purified by distillation at 65°C/20 mm Hg, leaving 75 grams (69% yield) of a colorless liquid. $[a]^{25} = -49.6°$ (1.3, $CHCl_3$), lit. reference[4]: $[a]^{22} = -48.6°$ (1.3, $CHCl_3$). Elemental Anal. Calcd. from $C_5H_9O_3$: C,50.8 and H,8.47. Found: C,49.33 and H,8.15. ^{1}H-NMR #3 (App. B): 1.22 (d, 3H); 2.45 (d,2H); 3.2 (s,1H); 0.70 (s,3H); 4.15 (m,1H). IR #4 (App.A): 3400 (s,br); 2950 (s,sh); 1710 (v.s); 1170 (s,br).

b. [R]-Benzyl ß-Hydroxybutyrate[6] [R]-methyl ß-hydroxybutyrate (73 g, 0.62 mol) and dry benzyl alcohol (300 mL; 2.89 mol) were transferred, under argon, into a flask equiped with a distillation apparatus. p-Toluenesulfonic acid (560 mg; 2.95 mmol) was added to the flask by removing the septum cap while flushing with argon. The solution was heated to 80°C, and the reaction was

carried out at this temperature for a continue procedure of: (1) 3 h under an argon atmosphere; (2) 1 h at 160 mm; (3) 3 h at 100 mm (most of methanol came out at this step) and (4) 2 h at 80 mm (little methanol came out at the end). The reaction contents were firstly diluted with diethyl ether (500 mL) and, then, extracted once with saturated aqueous $NaHCO_3$ (150 mL), twice with 5% aqueous $NaHCO_3$ (150 mL) and three times with brine (150 mL). After the solution was dried over $MgSO_4$, the ether and extra benzyl alcohol were removed by rotary evaporation (150 mm, 30°C) and vacuum distillation (0.2 mm, 50°C), respectively. The remaining crude oil was purified by vacuum distillation (90°C, 10^{-3} mm), obtaining 114 g (94% yield) of a colorless clear liquid. $[a]^{25} = -31.08°$ (5.0, $CHCl_3$). ^{1}H-NMR (#4): 1.21 (d,3H); 2.50 (m,2H); 4,25 (m,1H); 5,15 (s,2H); 7.35 (s,5H). IR spectrum (#5): 3400 (s,br); 3050 (m,db); 2900 (s,sh); 1710 (v.s,sha); 1160 (s,sha); 720 (s,db). Elemental Anal. Calcd.: C,68.02 and H,7.27. Found: C,67.79 and H,7.35.

c. [R]-Benzyl ß-O-Mesylbutyrate Dry pyridine (35 mL, 0.43 mol) and mesyl chloride (22 mL, 0.28 mol) were placed, through syringes, to a single-neck flask. This mixture had a deep red-brown color after being kept at 25°C for 15 min and -15°C for 30 min, respectively. The above cooled mixture was added, under argon at -15°C, to a solution of [R]-benzyl ß-hydroxybutyrate (41.5 g, 0.216 mol) in 220 mL of dry CH_2Cl_2. The reaction solution was maintained at approximately 5°C for 40 h, and then 25°C for 5 h under an argon atmosphere. The crystal precipitated out during the

reaction was removed by gravity filteration from the brown color solution. The filtrate was diluted with 600 mL of diethyl ether and, then, extracted each twice with 0.1N HCl (200 mL); 1N HCl (150 mL) (pH≥1.0); 5% aqueous $NaHCO_3$ (200 mL) (pH=8.5 after last extraction) and finally H_2O (200 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed, yielding 66 grams (98%) of a clear and yellow colored oil. $[a]^{25} = -19.25°$ (5.0, $CHCl_3$), ^1H-NMR (#5): 1.48 (d,3H); 2.70 (m,2H); 2.90 (s,3H); 5.13 (s,2H + m,1H); 7.35 (s,5H). IR (#6): 3050 (m,sha); 2900 (m,db); 1730 (v.s,sha); 1350 (v.s,br); 1170 (s,br); 910 (s,db); 720 (s,db). Elemental Anal. Calcd.: C,52.93; H,5.92. Found: C,53.29; H,5.99.

d. [R]-ß-O Mesylbutyrate [R]-benzyl-ß-O-mesylbutyrate (47.4 g, 0.174 mol), HBr (76 mL, 30-32 wt% in glacial acetic acid) and methylene chloride (80 mL) were transferred into a single-neck flask. The reaction was carried out, with stirring, at 25°C for 6 h and then maintained at -15°C for 16 h. The solvents were removed at 45°C under reduced pressure, using firstly a water aspirator for 1-2 h and then a vacuum pump (20 mm) for another 1-2 h, leaving a crude brown oil. Continued heating of this oil at 45°C resulted in degradation of the product. Flash chromatography (on 200 g of 230-240 mesh silica gel) eluted with chloroform (400 mL) and, subsequently, a mixture of chloroform/methanol (8/2), gaving 22.6 g (71% yield, in elution volume 550-900 mL) of a light yellow liquid after the solvent being evaporated. Purity of the fractionated product was moniterated by TLC. $[a]^{25} = -38.45°$ (5.0, $CHCl_3$). ^1H-NMR (#6): 1.48 (d,3H); 2.75 (m,2H); 3.00 (s,3H); 5.10

(m,1H). IR (#7): 3300 (s,dr); 2990 (s,br); 2600 (m,br); 1710 (v.s.,sha); 1330 (v.s,sh); 1160 (s,sha); 900(s,sha). Elemental Anal. Calcd.: C,32.97 and H,5.53. Found: C,33.24 and H,5.56.

e. [S]-ß-Butyrolactone[5-10] [R]-ß-O-mesylbutyrate (20.4 g, 0.11 mol) was placed in a beaker with 260 mL of H_2O. 11.0 g of $NaHCO_3$ was added to above solution slowly at 5°C, and the mixture was stirred to form a homogeneous solution with final pH of approximately 7.5. This solution was extracted twice with cold diethyl ether (100 mL) to remove unnuetralized organic phase and, then, the aqueous layer was transferred into a three-neck flask with 250 mL of methylene chloride. The two phase mixture was vigorously stirred, with an overhead stirrer, at 35°C for 2 h. The organic phase was separated out and extracted immediatly twice with 5% aqueous $NaHCO_3$ (120 mL) and three times with H_2O (120 mL). The aqueous layer was continually reacted with fresh methylene chloride (250 mL), at the same condition, for an additional 2 h, and the organic phase was treated identically as the first 2 h fraction. The two organic solutions, after extractions, were combined and dried over $MgSO_4$. A clear, yellow colored liquid was left after the solvent being removed. The crude product was distilled at 60°C/30 mm, through a short path distillator, yielding 5.1 g (54% yield) of a colorless liquid. This ß-butyrolactone was dried over CaH_2 and distillation again, as described above, just prior to the polymerization. $[a]^{25} = -26.1°$ (5.0, $CHCl_3$). ^{1}H-NMR (#7): 0.85 (d,3H); 2.28 (m,2H); 3.82 (m,1H). IR (#8): 2980 (m,db); 1820 (v.s.,sha); 1110 (s,sha); 1005 (m, ha); 800 (m,sha). Elemental

Anal. Calcd., C,55.81 and H,7.03. Found: C,55.20 and H,7.05.

3.3 Catalyst Preparations

All catalyst preparations were conducted in glassware which had been flame dried under reduced pressure while being alternately flushed with argon. Transfers of the liquid compounds were performed through cannulator or with a syringe, under an atmosphere of dry argon. Transfers of the catalyst powders were carried out in dry-box under inert atmosphere.

3.3.1 Determination of Et_3Al Concentration

Triethylaluminum solutions (1.9 M in toluene) were packaged under nitrogen in Aldrich Sure/Pac metal cylinders. The content of $AlEt_3$ from each cylinder was measured by the amount of ethane evolution when it reacted with water (Figure 3.1). The procedure used was as follow: 1.0 mL of the commercial $AlEt_3$ solution was diluted with 49 mL of dry THF, from which 10 mL was then transferred to a 50 mL three-neck flask. Then, 5 mL of water was added dropwise, through a dropping funnel, while cooling the reaction flask with an external ice-water bath. The volume of the gas evolution was measured by displacement of the mineral oil in the volume graduated cylinder which was attached to the flask. The final volume (approximately 30 mL) was measured and recorded after proper time at the same temperature. This procedure was repeated three times for each solution purchased. The average

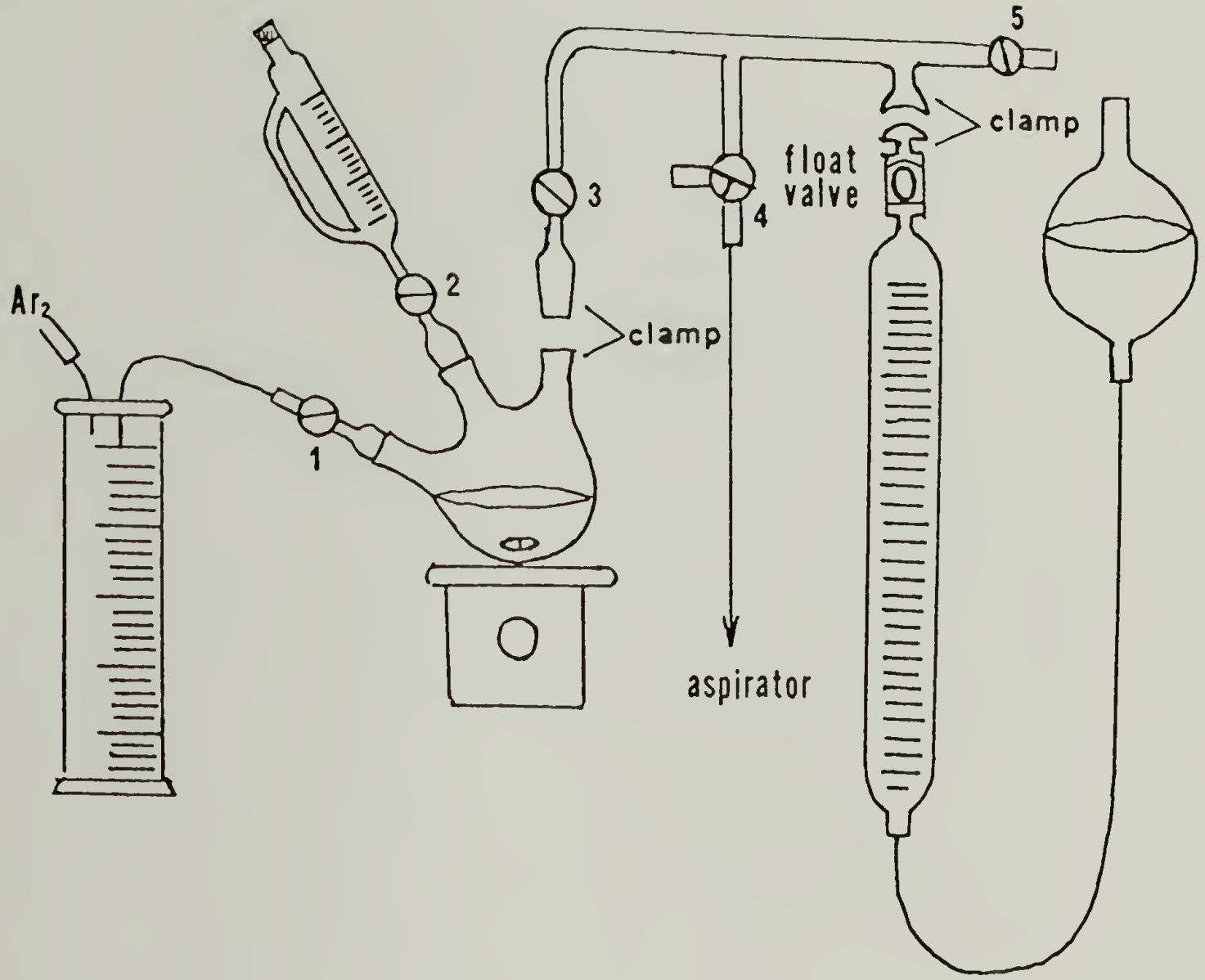

Figure 3.1 The instrument desigh for determination of the $AlEt_3$ (in tolune) concentration

molarity of the $AlEt_3$ solution was 1.9 ± 0.1 M. This measured value was used quantitatively for the catalyst preparations.

3.3.2 "*In-situ*" Preparation of $AlEt_3/H_2O$

The *"In-situ* Catalyst"[11-12] was prepared by firstly adding the $AlEt_3$ solution to the polymerization ampule, cooling it to -78°C and then injecting a known volume of water. The reaction was carried out at this temperature with magnetic stirring for half a hour and, then, the catalyst solution was warmed to room temperature. The catalyst solution usually contains both gel-like translucent and white particles in a colorless solution.

3.3.3 Ethylaluminoxane (EAO), Methylaluminoxane (MAO) and Iso-Butylaluminoxane (IBAO)

The oligomeric EAO catalyst was prepared in a procedure very similar to that described previously.[13] Toluene (86 mL) and 1.9 M $AlEt_3$ solution (30 mL, 0.57 mol) were combined in a flask which was cooled with an external bath at -78°C. Deionized water (1.06 mL, 0.059 mol) was added slowly into the solution, and the system was vigorous stirred for 40 min at this temperature. The reaction was completed at 0°C for another 30 min., and the resulting suspension was warmed to room temperature to allow the particles to be settled. The clear supernatant was transferred, under argon, into a distilling flask from where toluene was removed at 10^{-1} Torr. Anhydrous decahydronaphthalane (decalin, 100 mL) was, then, added to the reaction residue and distilled away together with free

$AlEt_3$ and the dimer under vacuum 10^{-3} Torr at 60°C. Continually, the system was heated to 180-190°C for 30 min at 10^{-3} Torr and then cooled to room temperature under argon. Above procedure of decalin and high temperature treatment was performed twice. When the second distillation was visually complete, the residue was subjected to a vacuum for an additional 90 min at 60°C/10^{-3} Torr, leaving a ceramilike solid. This residue was dissolved in anhydrous hexane (100 mL) and stirred for 2 h with a little bit heat. After removing the insolubles by filting through a 4-8 μm sintered glass funnel, a clear and colorless solution was yield. Hexane was then removed under a reduced pressure, leaving 2.2 g (52% yield) of a white powder. Elemental Anal. Calcd. for C_2H_5AlO unit: C,33.3; H,6.94 and Al,37.5. Found: C,29.3; H,6.92 and Al,39.2. ^{1}H-NMR (#8): 0.35 (b,s,2H) and 1.30 (b,s,3H). The molecular weight of the EAO catalyst was measured using a Knauer model 11 vapor pressure osmometer (VPO) in a dry box. The instrument was calibrated by benzil using dry benzene as solvent. The number of repeating unit (N) in the oligomer $[-Al(Et)-O-]_n$ was determined to be 16.

The MAO catalyst was prepared in the laboratory of Professor J. C. Chien at Univ. of Massachusetts.[10] Elemental Anal. Calcd. for CH_3AlO: C,20.9; H,5.2 and Al,46.6. Found: C,23.6; H,7.1 and Al,46.5.

The oligomeric IBAO catalyst with average repeating unit of 14 was purchased from Shering Chemical Co. in west Germany and was used without purification.

The catalyst solutions of EAO, MAO and IBAO were prepared by dissolving the corresponding solid in dry toluene (0.5 mmol/mL),

giving the colorless solution for each catalyst.

3.3.4 Diethylzinc Water Catalyst Et_2Zn/H_2O

The preparation of Et_2Zn/H_2O (1:0.6) catalyst is similar to that previously described in the literature.[12-13] In a 50 mL single neck flask, 15 mL dry 1,4-dioxane and 3.5 mL Et_2Zn (neat, 32.4 mmol) were combined at 0°C. H_2O (0.37 mL, 20.5 mmol) was then added dropwise at this temperature, and the mixture was stirred under argon for 15 min. After an additional 1 h reaction at 25°C, the volatiles were removed at 10°C/10^{-1} mm Hg, leaving 1.5 g of a yellow powder. The product was dissolved in toluene (31 mg/mL), giving a yellow catalyst solution with some insoluble particles.

All the EAO, MAO, IBAO and Et_2Zn/H_2O catalysts were stored as solids inside tightly caped bottles under an argon atmosphere in a dry-box, using Drearier as desiccant. The catalysts were usually used within a month of their preparation and the catalyst solutions were used within 24 h.

3.3.5 (5,10,15,20-Tetraphenylporphinato) Aluminum Chloride, (TPP)AlCl[14-15]

$TPPH_2$ (1 mmol) was placed in the catalyst flask shown in Figure 3.2. Methylene dichloride (CH_2Cl_2, 30 mL) was introduced to dissolve $TPPH_2$, and then Et_2AlCl (0.15 mL, 1.2 mmol) was added in 20% excess to $TPPH_2$. The reaction mixture was allowed to stand for about 1 h, with magnetic stirring, under argon at room temperature. From the above reaction mixture, volatile materials

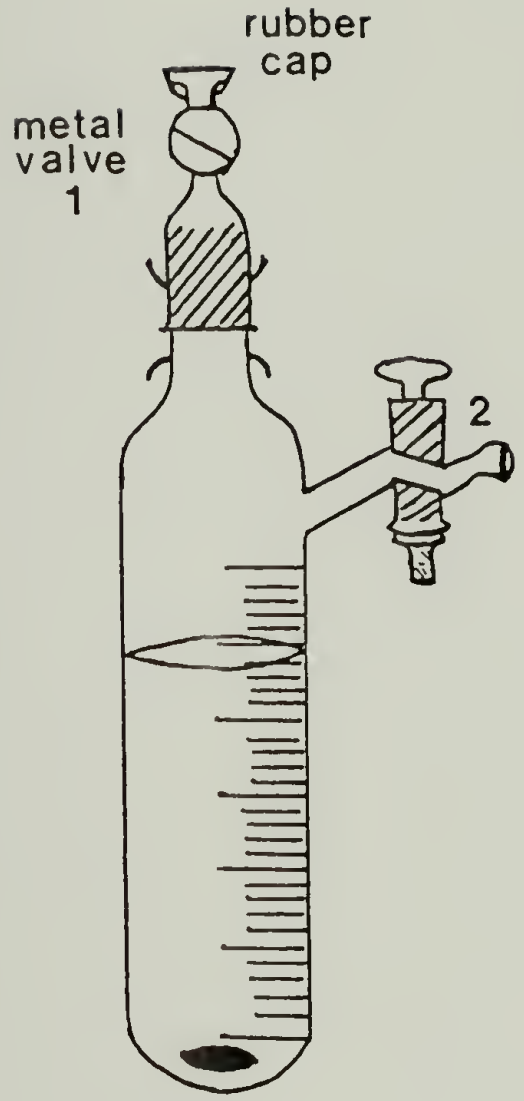

Figure 3.2 The flask for catalyst preparation.

were removed under reduced pressure, leaving a purple solid TPPAlCl with a metallic luster. Dry toluene (40 mL) was then added to dissolve TPPAlCl, giving a purple homogeneous solution.

3.3.6 Tetraethyl Aluminoxid, $(Et_2Al)_2O$[16-18]

This catalyst was prepared by two step reactions shown bellow. Both steps are in 1:1 equimolar reactions.

$$AlEt_3 + LiOH \longrightarrow Et_2AlOLi + EtH \quad (1)$$

$$Et_2AlOLi + ClAlEt_2 \longrightarrow (Et_2Al)_2O + LiCl \quad (2)$$

To a suspension of LiOH (2.4 g, 0.01 mol) in m-xylene (40 mL), a slightly less than equimolar quantity of $AlEt_3$ (13.4 mL, 0.098 mol) was added dropwise at 80°C to maintain a vigorous evolution of ethane. The reaction was completed under refluxing, and the solution was filtered under argon. The filtrate was concentrated under reduced pressure, and n-Hexane was then added to precipitate the by-product I (Et_2AlLi, $AlEt_3$). This procedure was repeated several times to ensure complete removal of I. On evaporation of the filtrate at 20 mm Hg pressure, 3.6 grams of a white ceramilike solid was obtained (34% yield). Elemental Anal. Calcd.: C,44.4; H,9.25; Al,25.0 and C/Al,2.00. Found: C,42.5; H,8.69; Al,24.95 and C/Al,1.91. ^1H NMR (in dry C_6D_6): 1.42 (s,3H) and 0.18 (s,2H).

To a solution containing 2.7 g (0.025 mol) of Et_2AlOLi in 50 mL of toluene, 3.1 g (0.026 mol) Et_2AlCl was added dropwise over 20 min at -20°C, and the reaction was completed at 20°C in 2 h.

Precipitated LiCl was removed by filtration. From the resulting colorless solution, toluene was evaporated carefully under reduced pressure (≥10 mm Hg, at room temperature). Upon addition of 70 mL of hexane to the residue, a small amount of LiCl was precipitated and removed again. Evaporation of the clear solution resulted in an oily liquid (a little bit cloudy). Elemental Anal. Calcd.: C,51.58; H,10.83; Al,28.98 and C/Al,2.00. Found: C,48.35; H,9.85; Al,27.15 and C/Al,2.08. ^{1}H NMR (in dry C_6D_6): 1.28 (s,3H) and 0.14 (s,2H). Molecular weight of the product was 257 (theoretical 186) measured by VPO in dry benzene, using benzil ($\bar{M}_n$ = 210.23) as the standard.

3.4 Polymer Preparations

3.4.1 General Procedure

The ampoule used in the polymerization was attached to a vacuum manifold and flame dried under vacuum while being alternately flushed with argon. All the reactants and solvent were transferred with syringe under argon atmosphere. After the catalyst solutions being prepared or transferred into the ampoule, the monomers were added at -78°C. The contents of the ampoule were, then, degassed during three freeze-thaw cycles and finally sealed under vacuum. Polymerization reactions were carried out at 60°C for the time period ranging from 7 to 80 days depending on the catalyst system.

3.4.2 Polymer Purification and Fractionation

At the end of polymerization period, the polymers were usually yellow in color if they were synthesized with the $AlEt_3/H_2O$ and/or Et_2Zn/H_2O catalysts, and those with the TPPAlCl catalyst were purple or brown. After the ampoules being opened, the contents were precipitated in ether containing 1% water. The precipitates were vacuum filtered and, then, dissolved in chloroform. After being stirred at room temperature for 16 h and refluxed for 10 min., the hot chloroform suspension was passed through a 25-50 μm sintered glass filter funnel containing a 1 cm layer of celite. The clear chloroform solution obtained was then concentrated and precipitated into ether again, yielding the crude product after being filtered and washed with ether. The crude polymers were stirred with acetylacetone (AcAc) (7.5 mL/g of crude product) at room temperature for 24 h to remove the organometallic materials.[13] The polymers in AcAc solution were precipitated in methanol and vacuum dried, yielding the AcAc-treated product.

The latter products were then separated into the acetone-soluble and the acetone-insoluble fractions by the following procedure. The polymer samples to be fractionated were ground in mortars, quantitatively transferred into extractor thimbles and extracted with acetone in Soxlet extractors for more than 16 h. The acetone insoluble fractions of the polymers remained in the thimbles while the acetone soluble fractions were obtained after solvent removal.

3.4.3 Polymer Characterization

The molecular weights of polymers reported in this work were determined by GPC. The instruments used included a Waters Model 6000A solvent delivery system and a Model 401 refractive index detector with 106, 105, 104, 103, and 500Å ultrastyragel columns in series. Chloroform was used as eluent at a flow rate of 1.4 mL/min. Sample concentration of 0.2% wt/vol and injection volumes of 300 μL were used. Polystyrene standards with a low polydispersity were purchased from Polysciences and used to generate a calibration curve.

^{13}C NMR and ^{1}H NMR spectra were recorded at 75.4 and 200 MHz on a varian XL-300 and 200 NMR spectrometers, respectively. The sample concentrations employed for ^{13}C NMR measurement were typically 4.0% wt/vol. All the polymer spectra were recorded at 25-30°C by using $CDCl_3$ as solvent. $CDCl_3$ and tetramethylsilane (TMS) were used as internal references for ^{13}C and ^{1}H NMR spectrum, respectively. The delay time between sampling pulses for both ^{13}C and ^{1}H NMR measurements were 3.0 s. Quantitative analyses for copolymer compositions were performed by ^{1}H integration and were reported as relative intensities of hydrogen. The following descriptions were used for the routing presentation of ^{1}H spectra: s, single; d, doublet; m, multiplet.

The heat fusions (ΔH_m) and melting temperatures (T_m) of all polymer samples were determined by using a Perkin-Elmer Model DSC-4. The weight of each sample in DSC measurement was typically 4-8 mg, and the heating rate used was 20°C/min. The

second scan was usually done at the same heating rate as the first scan, after a quick cooling. T_m was taken at the maxima of endothermic peak.

IR and Fourier transfer inferred (FTIR) were recorded on Perkin-Elmer Model 283 and Mattson CYGNUS 100 spectrometers, respectively. The following descriptions were used for the routing presentation of IR spectra: s, strong; v.s., very strong; m, medium; br, broad; sh, shoulder; sha, sharp; db, doublet.

Aluminum and C, H analyses were carried out in the Microanalysis Laboratory at University of Massachusetts, Amherst.

3.4.4 Polymerization of [R,S]-ß-Butyrolactone

Conditions for the polymerizations using the *"In-situ* Catalyst" $AlEt_3/H_2O$ and alkylaluminoxanes were summarized in Table 2.2-a. Elemental Anal. Calcd. for PHB unit $C_4H_6O_2$: C,55.80 and H,6.98. Found (Sample 7): C,54.85 and H,6.74. Analyses of aluminum contents in the polymers before and after purification are shown in Table 2.3. FTIR, ^1H NMR and ^{13}C NMR spectra of the synthetic PBL (Sample 5): Fig. 2.13, Fig. 2.18-a and App.C #2, respectively. The typical peak melting points of the synthesized polyhydroxybutyrates were 159-166°C. The enthalpy of fusions were 10 (±2) and 16 (±2) cal/g for AcAc treated and acetone-insoluble fractions of P([R,S]-HB), respectively.

The polymerizations catalyzed by Et_2Zn/H_2O and TPPAlCl were carried out at 60°C in 5 and 30 days, respectively. All the polymer products using these two catalysts were atactic and

amorphous. Therefor, AcAc treatment and acetone extraction were not used for these samples. ^{1}H NMR spectra for these atactic PBLs were as same as those using the $AlEt_3/H_2O$ catalyst. ^{13}C NMR (Sample 9): Fig. 2.11.

3.4.5 Polymerization of [R,S]-Benzylmalolactonate

Table 2.8 showed the conditions and yields for the polymerizations using the $AlEt_3/H_2O$ catalysts. Elemental Anal. Calcd. for PBML unit $C_{11}H_{10}O_4$: C,64.07; H,4.85. Found (Sample 17): C,62.92; H,4.82. Aluminum contents in the PBML samples before and after their purifications are shown in Table 2.3. FTIR, ^{1}H NMR and ^{13}C NMR spectra of PBML-17: App.A.#9, Fig.2.18-b and App.C.#3, respectively. The melting temperature of these synthetic PBML were ranged from 147-195°C, and the peak melting points were about 180 and 185°C for the unfractionated and acetone-insoluble fractions, respectively. The values of enthalpy of fusion were 4.0 (±1) and 6.5 (±1) cal/g for the AcAc treated and acetone-insoluble fractions of P([R,S]-BML), respectively.

3.4.6 Hydrogenation of Poly([R,S]-Benzylmalolactone)

2.0 g of PBML (9.7 mmol of the repeating units) were dissolved in a mixture solution of 120 mL of acetyl acetate and 40 mL ethanol (90%), in a 250 mL single-neck flask containing a magnetic stir bar. 800 mg of 10 wt% palladium (0.9 mmol Pd) on active carbon was added, and the flask was, then, attached to the

hydrogenolysis apparatus shown in Fig. 3.3. The operation of the apparatus was described previously.[19] The suspension was stirred at 35°C, and hydrogen was admitted. The uptake of hydrogen was monitored by water displacement and no more hydrogen was being consumed after 6 h. The palladium catalyst was then removed by suction filtration through celite. After the solvent being evaporated, about 20 mL of the polymer solution was left, and it was then added dropwise into 500 mL of ether. The polymer was isolated by suction filtration and dried in vacuum at room temperature for 4 h. 0.7 grams of polymer were obtained (64% yield). Elemental Anal. Calcd.: C,41.4 and H,3.47. Found: C,42.5 and H,3.85. IR spectrum (#10): 3150-2400 (OH stretch-hydrogen-bonded); 1740 (ester C=O stretch); 1600 (carboxyl C=O stretch--hydrogen bonded); 2370 and 1190 (c-O stretch). ^{1}H NMR (#8): 2.85 (m,2H); 5.30 (m,1H) (1 wt% solution in deuterium acetone). The hydrogenolysized polymer product (PMA) was soluble in H_2O, methanol, acetone and THF but $CHCl_3$ while the polymer before hydrgenolysis was only soluble in $CHCl_3$. The PMA product was decomposed at 185°C.

3.4.7 Copolymerization of BL and BML

The copolymerizations were carried out for 14, 27, and 60 days in the $ZnEt_2/H_2O$, AlR_3/H_2O, and TPPAlCl catalyst systems, respectively. The copolymer products synthesized with the AlR_3/H_2O catalysts were extracted with acetone to obtain the acetone-soluble and -insoluble fractions. The compositions of the

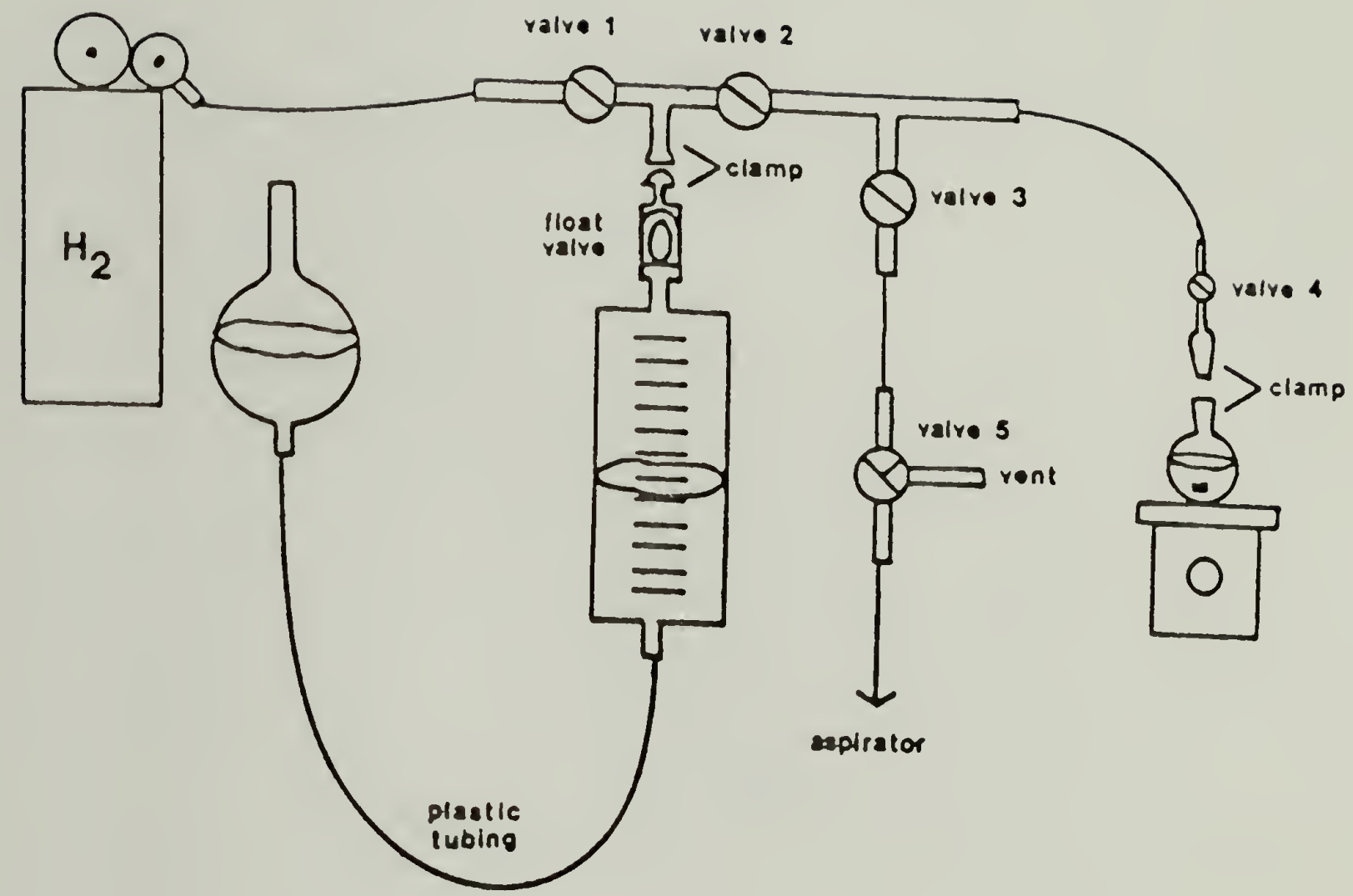

Figure 3.3 Hydrogenolysis apparatus.

copolymers were determined by ^{1}H NMR spectroscopy as shown in Fig. 2.18-c. The comonomer sequences were observed by ^{13}C NMR spectroscopy, as shown in Fig. 2.23, especially by the expansions of methylene carbon region (see Fig. 2.24). The peak melting temperature of the copolymers after AcAc treatment were about 156°C, and the values of enthalpy of fusion were between 0.3 to 2.1 cal/g. Aluminum contents in the copolymers were shown in Table 2.3. Elemental Anal. calcd. for Copolymer 34 (HB:BM=83:17): C,57.21 and H,6.66. Found: C,56.84 and H,6.10. Elemental Anal. calcd for Copolymer 35 P(HB-co-MA), which was obtained by hydrogenation of Copolymer 34,: C,53.36, H,6.42. Found: C,53.29, H,6.18.

3.4.8 Preparations of Optically Active P([R]-HB) and P([S]-HB)

The polymerizations of [S]-ß-BL with the catalysts of "*In-situ*" $AlEt_3/H_2O$ (1:1), EAO, $ZnEt_2/H_2O$ (1:0.6), and $(Et_2Al)_2O$ were performed in the same conditions as described previously for that of [R,S]-BL,[20] and the results are summarized in Tables 2.9.

Since the polymer synthesized using the EAO catalyst has a relative low specific rotation, it was further fractionated[21] in the following methods. The polymer was firstly dissolved in $CHCl_3$ with a concentration of 0.25 wt%. Methanol, as a non-solvent, was then added slowly until the cloudy point[21] while the solution was vigorously stirred. The first precipitated polymer, which was the high molecular weight fraction, was separated from the filtrate by gravity filtration (30 wt%). Additional methanol was continually added to the filtrate, as described above, providing a second

precipitated polymer which is referred as the middle molecular weight fraction (50 wt%). As the remaining filtrate being concentrated by rotoevaporation, it was reprecipitated in methanol, giving a low molecular weight polymer fraction (20 wt%).

3.5 Degradation of the Optically Active Polymers by Methanolysis

A synthetic optically active polymer was dissolved in dry $CHCl_3$ (0.1 g/15 mL) in a pyrex culture tube, with a teflon-lined screw cap. Under an argon atmosphere, 15 mL of methanol with 3% (v/v) H_2SO_4 was added to this solution and the mixture was, then, heated in an external oil bath of 100°C for 4 h. Subsequently, a one-half saturated aqueous NaCl solution (8 mL) and diethyl ether (15 mL) were added to and well mixed with above solution in a separator funnel. The two layers were separated and the aqueous layer was extracted three times with ether. The combined ether solution was, then, washed with saturated aq. $NaHCO_3$ and NaCl solutions, respectively, to a final pH of 6.5. After drying over $MgSO_4$, the solvents were removed under reduced pressure. The yields of the degraded [R] or [S] MHBs were about 90%.

3.6 Optical Purity Measurements

3.6.1 ^{1}H-NMR Spectra with an Europium Shift Regent[22]

A stock solution of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium

($Eu(hfc)_3$) was prepared by dissolving 275 mg (0.23 mmol) of it in a mixture of 4.5 mL of spectroscopy grade carbon tetrachloride and 0.5 mL of deuterated benzene (90:10). The deuterated benzene contained 0.5% (v/v) TMS was used to spin lock the instrument. A specific weight of optical active compounds was dissolved in 1.0 mL (0.46 mmol/mL) of the $Eu(hfc)_3$ stock solution.

3.6.2 Specific Rotations

Optical rotations were recorded on a Perkin-Elmer 141 polarimeter in a temperature equilibria cell. The values of optical rotations reported in this work are described as follow: $[a]^{\circ}C_{nm}$ = specific rotation (concentration in g/100 mL, solvent). All the polymer samples were measured at wavelength at 365 nm (Hg), and the natural origin P([R]-HB) was used as the standard. The optical purity of [S]-ß-BL and the degradation products methyl hydroxybutyrate (MHB) were measured at 589 nm (Na).

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CHAPTER 4

RECOMMENDED FUTURE WORK

1. Since we have successfully prepared the [S]-ß-butylactone and [R]-ß-benzyl malolactone with high optical purities, it is possible to obtain the optically active copolymer P(HB-co-BML), in either R or S configuration, by copolymerizing above two monomers with proper catalysts. Both of these stereoisomers will be important in the further study obout the biodegradability of the materials.

2. It will be interesting if we can prepare the stereoblock PHB copolymers in the different ratios of [R]/[R,S]-HB units, so we can understand better: (a) the effect of amount of racemic PHB units on the polymer's biodegradability and (b) the possible biodegradation positions in the copolymers.

3. It is worth to study the mechanism of the ring-opening polymerization reaction with ^{18}O labelled ß-BL in [R] or [S] configuration. By using the method of ^{18}O-NMR spectroscopy, it is possible to know the modes of the ring-opening reactions with different organometallic catalysts and, therefore, to imagine the coordination structures between the lactone and catalysts.

4. In order to prepare the high molecular weight poly(ß-substituted ß-propiolactones) with narrow molecular weight distributions, it is interesting to try the living polymerization of these lactones with various methal alkoxides, such as aluminum

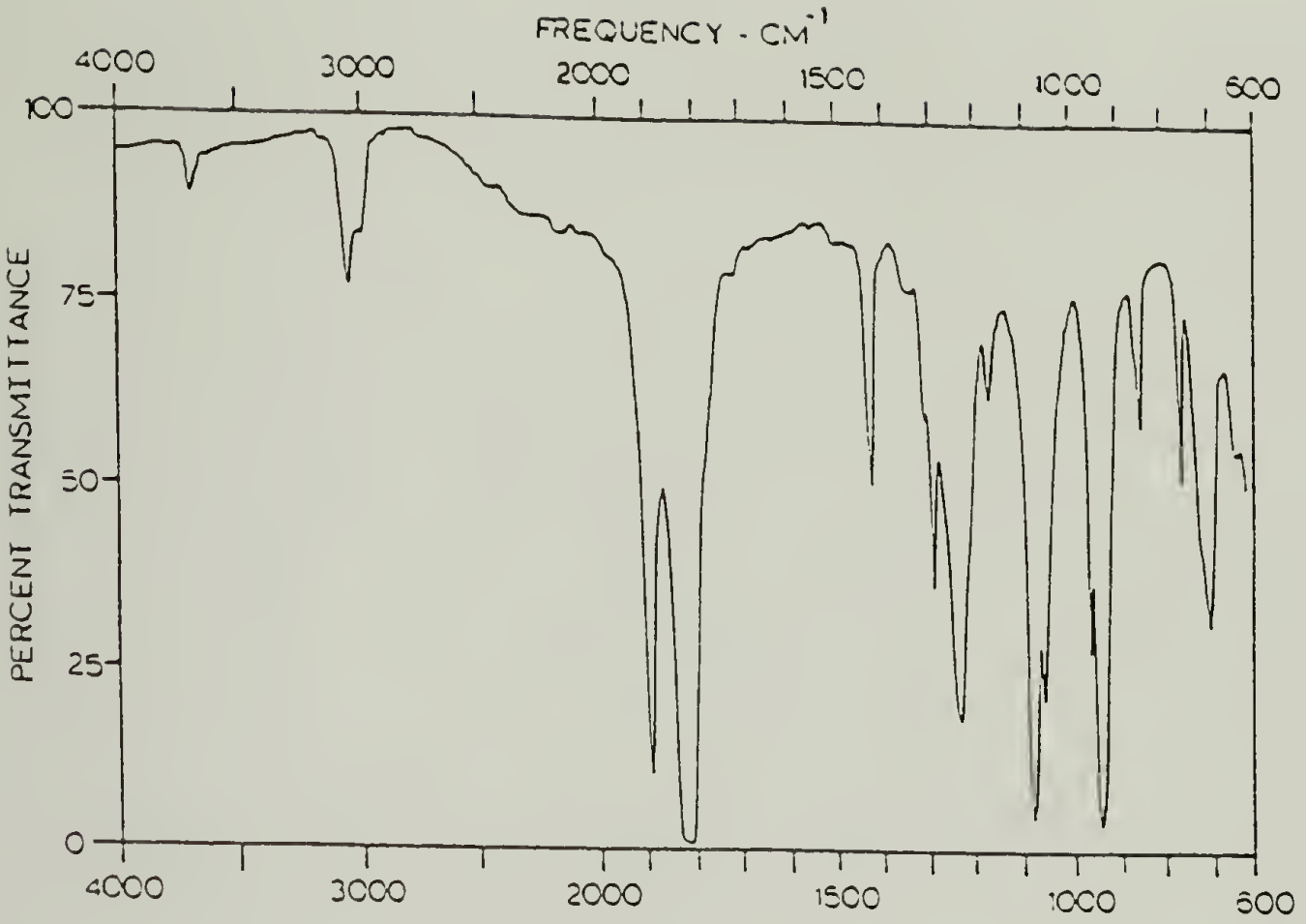
triisopropoxide, $Al(OiPr)_3$, since this kind of initiator has shown a living character in the polymerizations of four different lactones.* The result, then, can be compared with the polymerization with the AlTPPCl catalyst, the latter is less efficient for the ß-propiolactones with bulkier substituted groups.

5. It would be wonderful if we can obtain a good chiral catalyst to polymerize stereoselective PHB or PBML from the racemic monomers because it is very expansive to synthesize those optically active monomers experimentally.

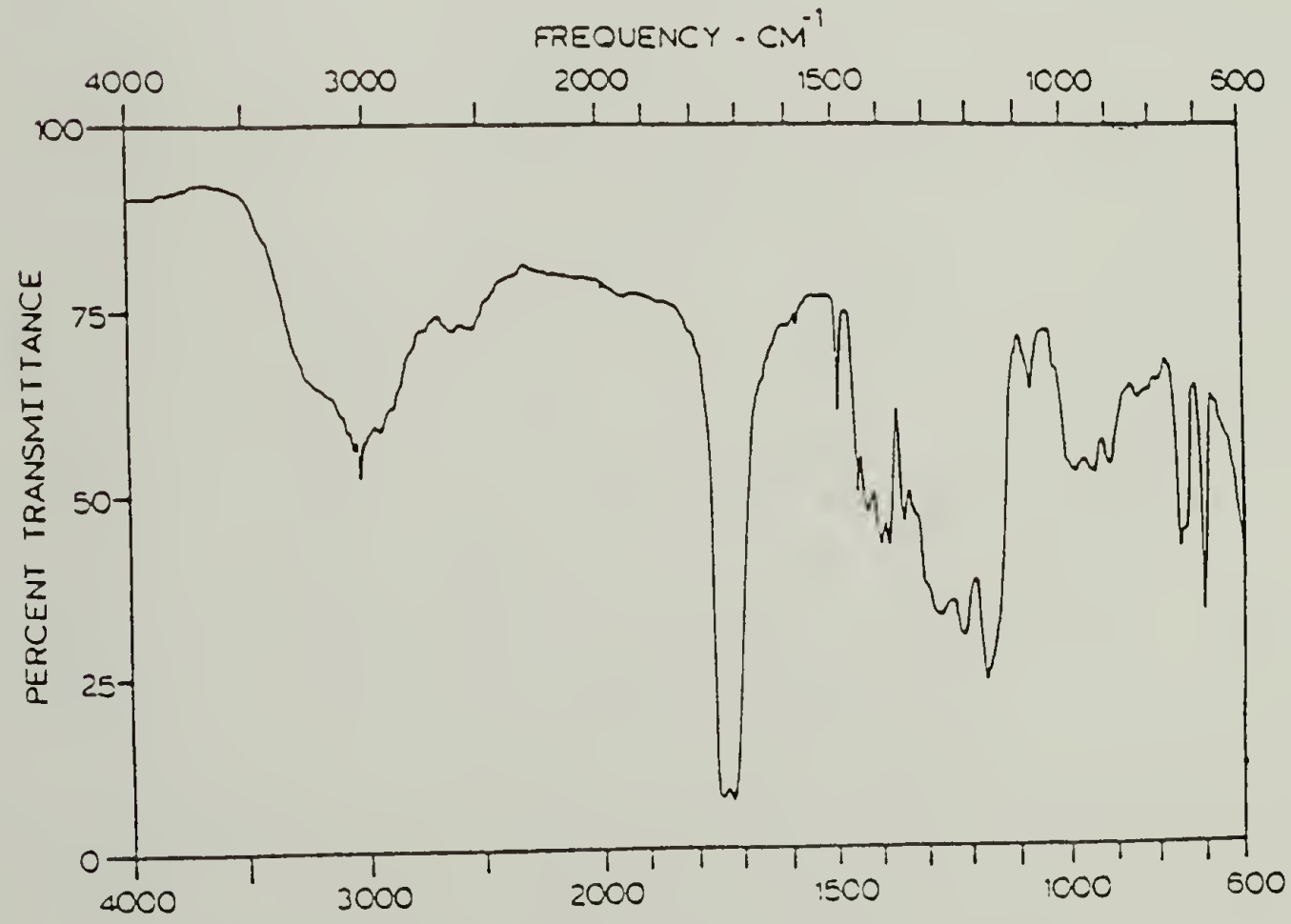
* Kricheldorf, H.R., Berl, M. and Scharnagl, N., *Macromolecules*, 1988, 21, 286-293.

APPENDICES A

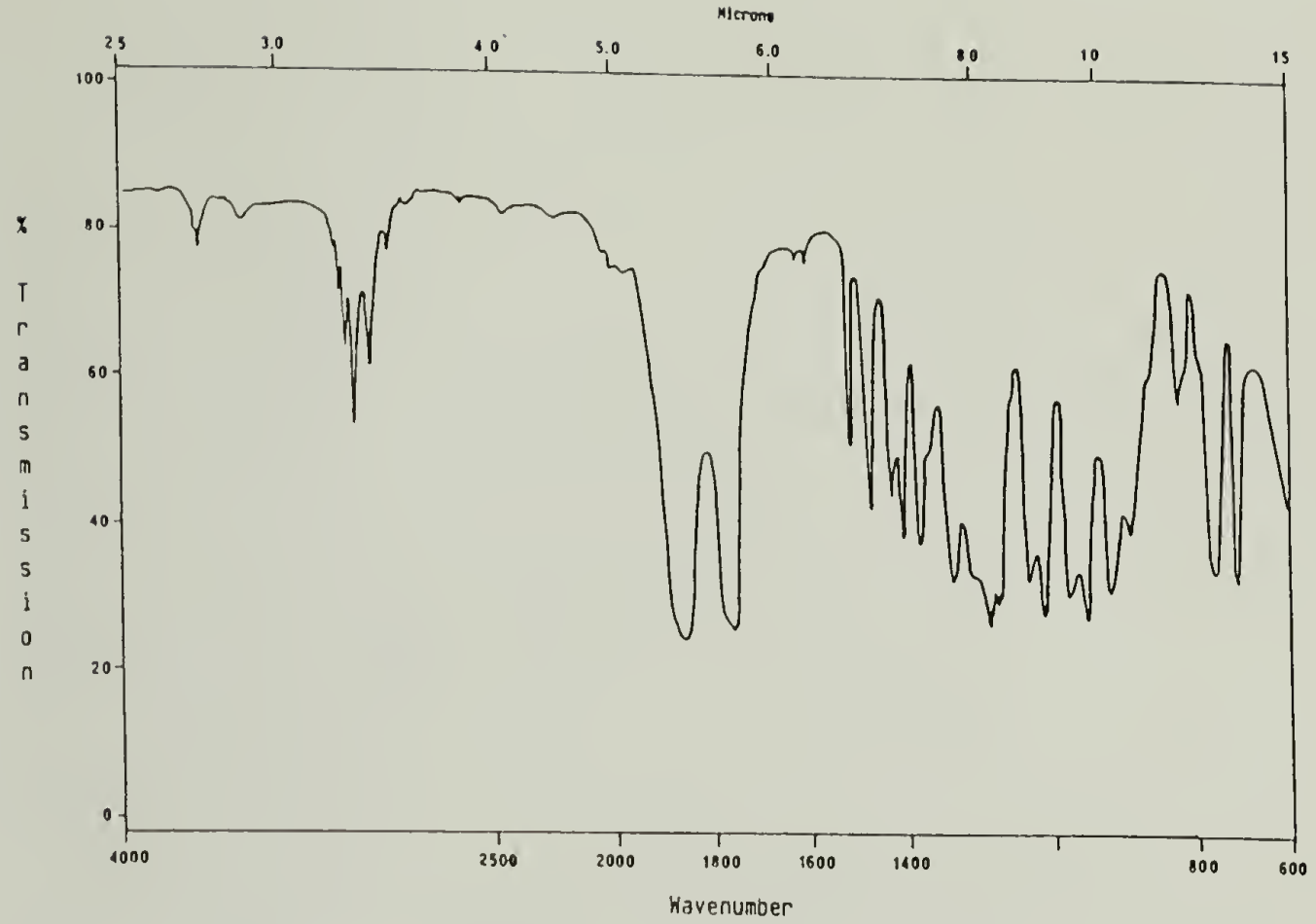
INFRARED AND FTIR SPECTRA



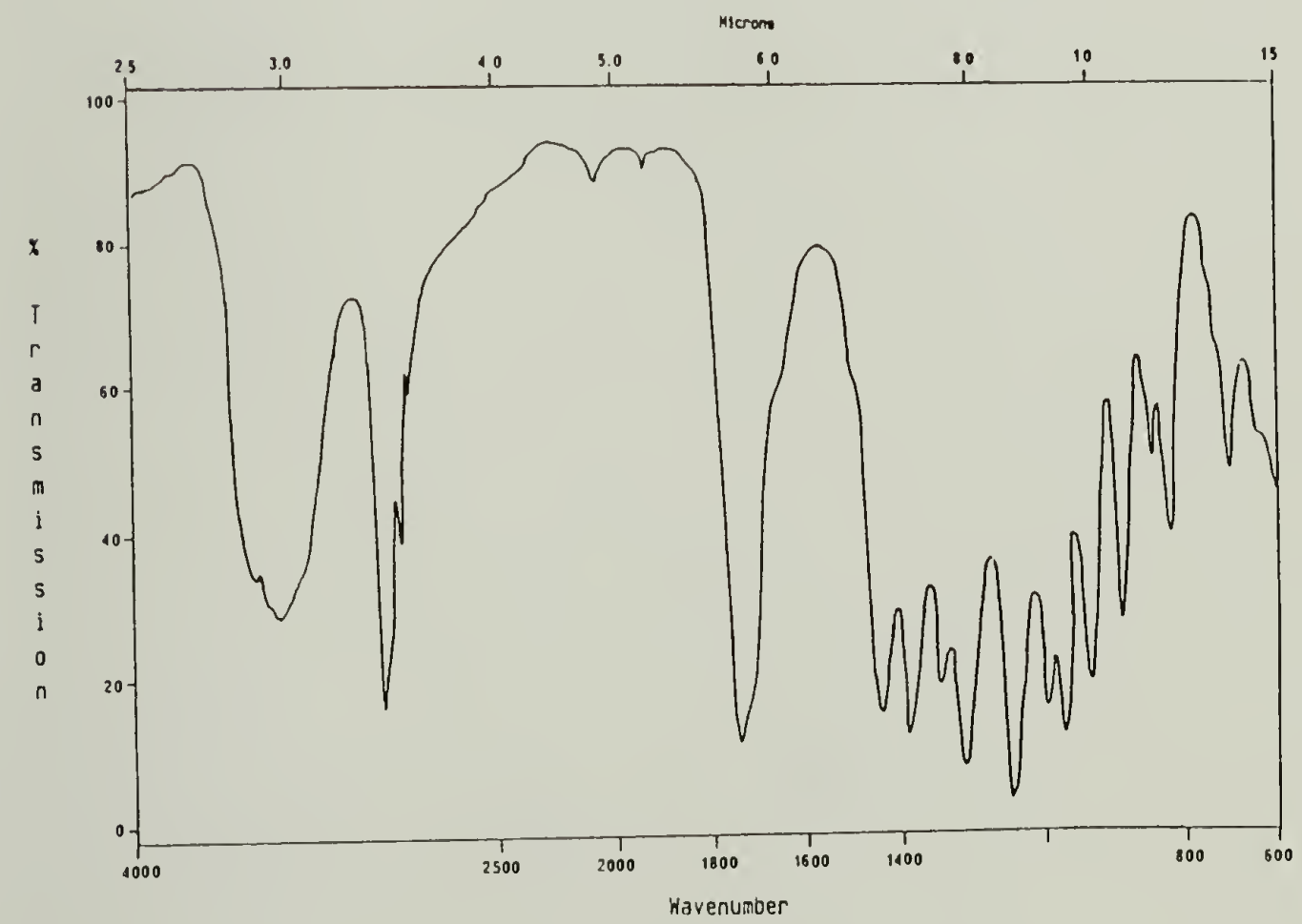
IR Spectrum No. 1 BROMOSUCCINIC ANHYDRIDE



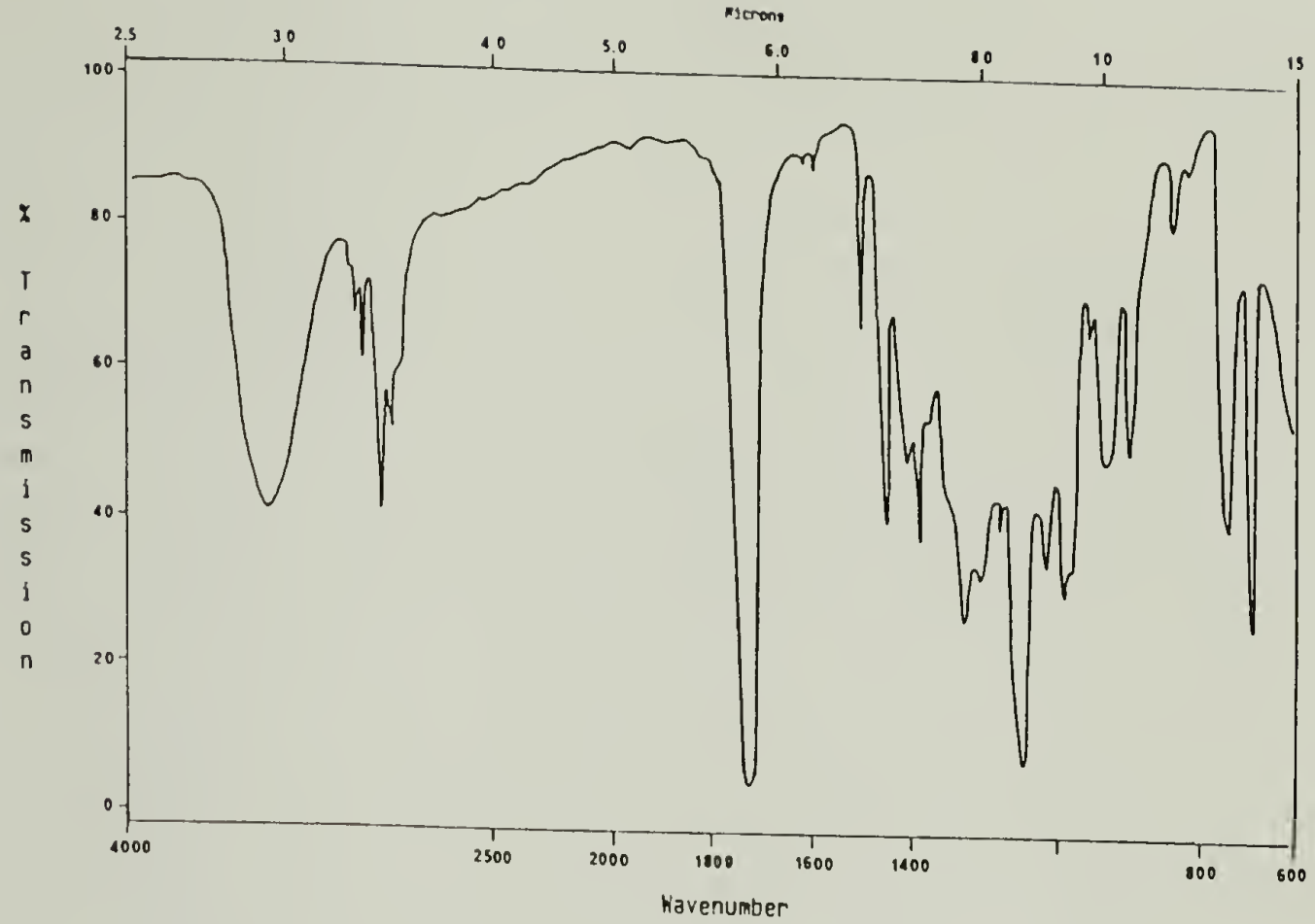
IR Spectrum No. 2 BENZYL BROMOSUCCINATE(S)



IR Spectrum No. 3 BENZYLMALOLACTONE



IR Spectrum No. 4 METHYL-[R]-β-HYDROXYBUTYRATE



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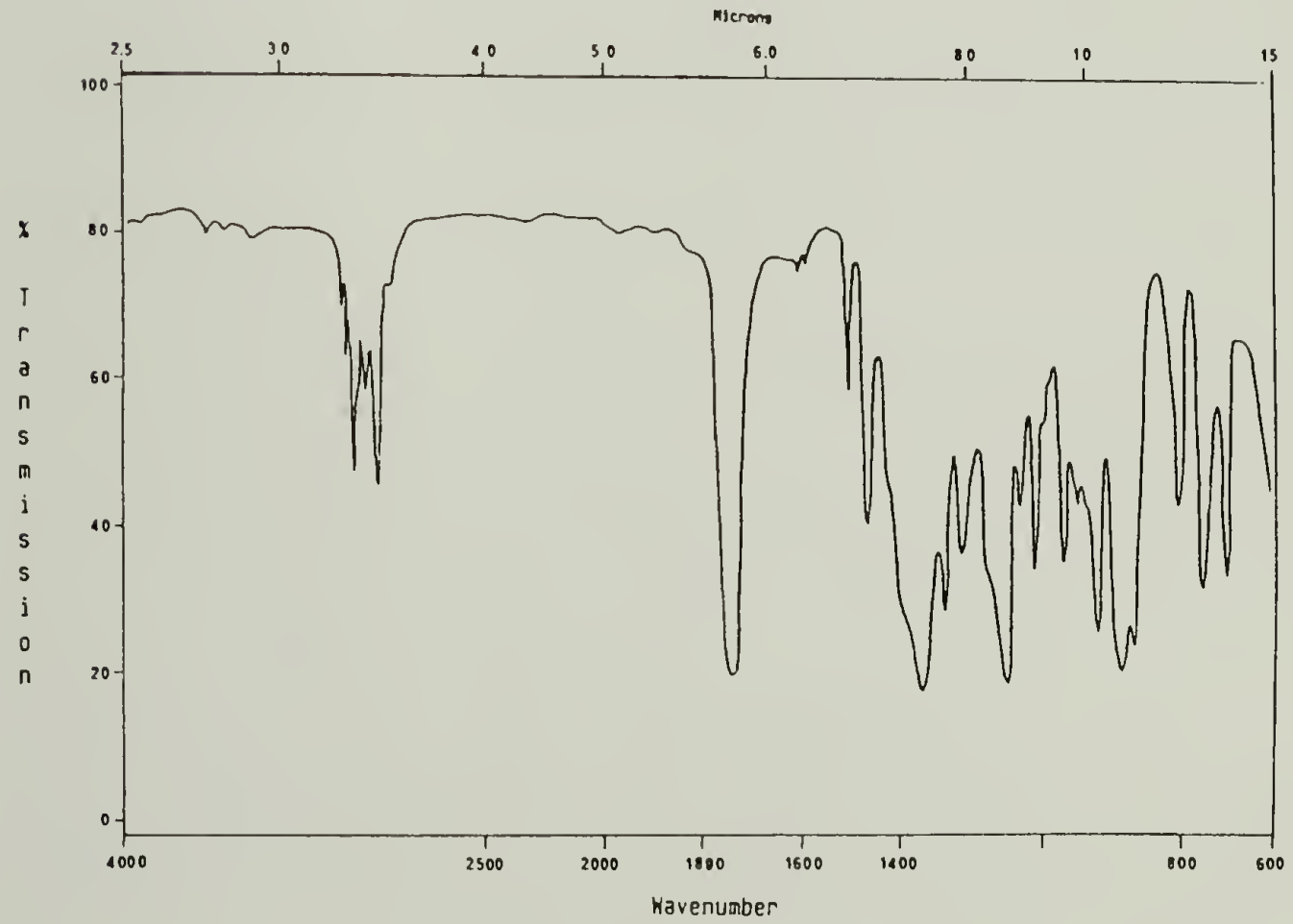
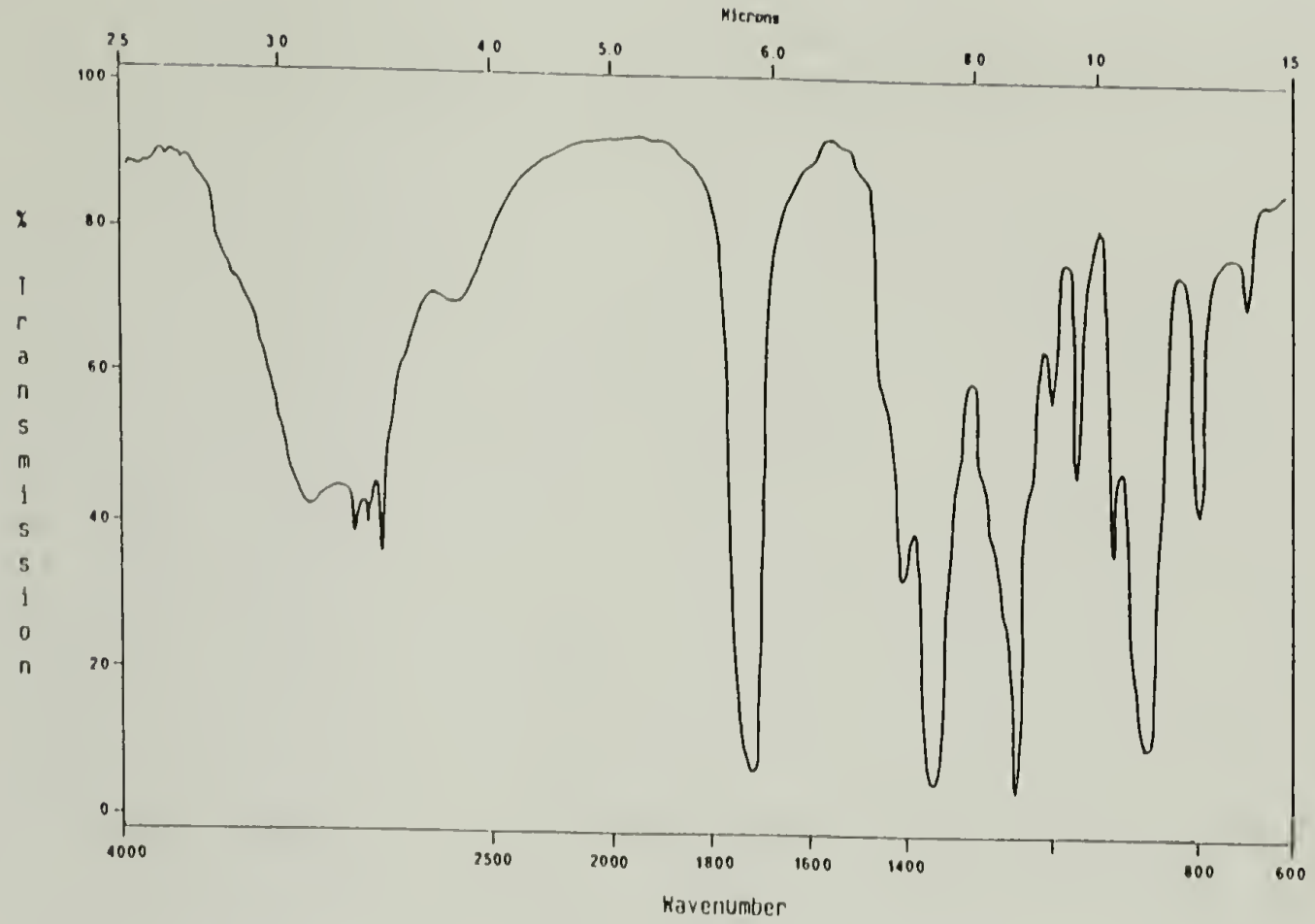
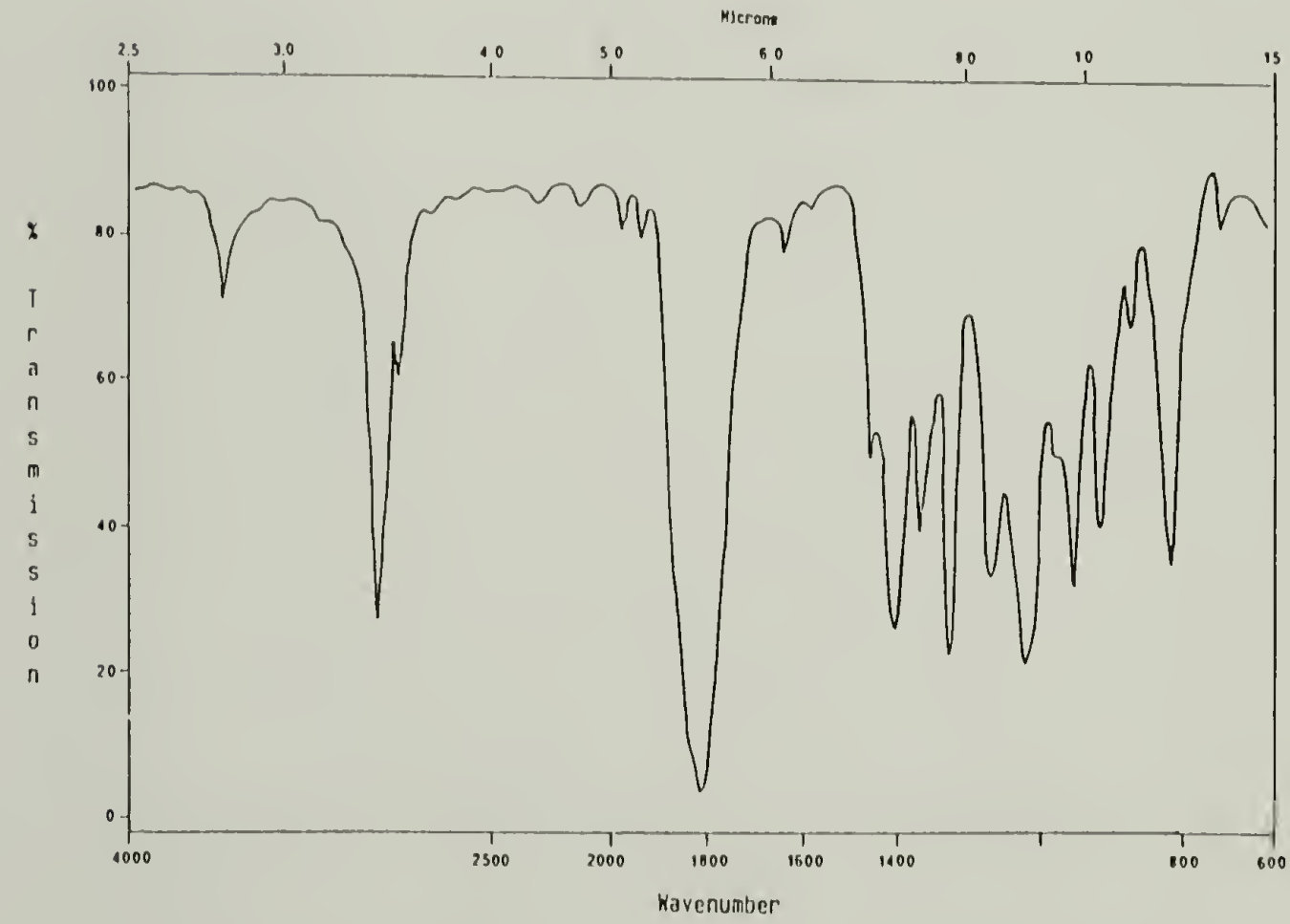


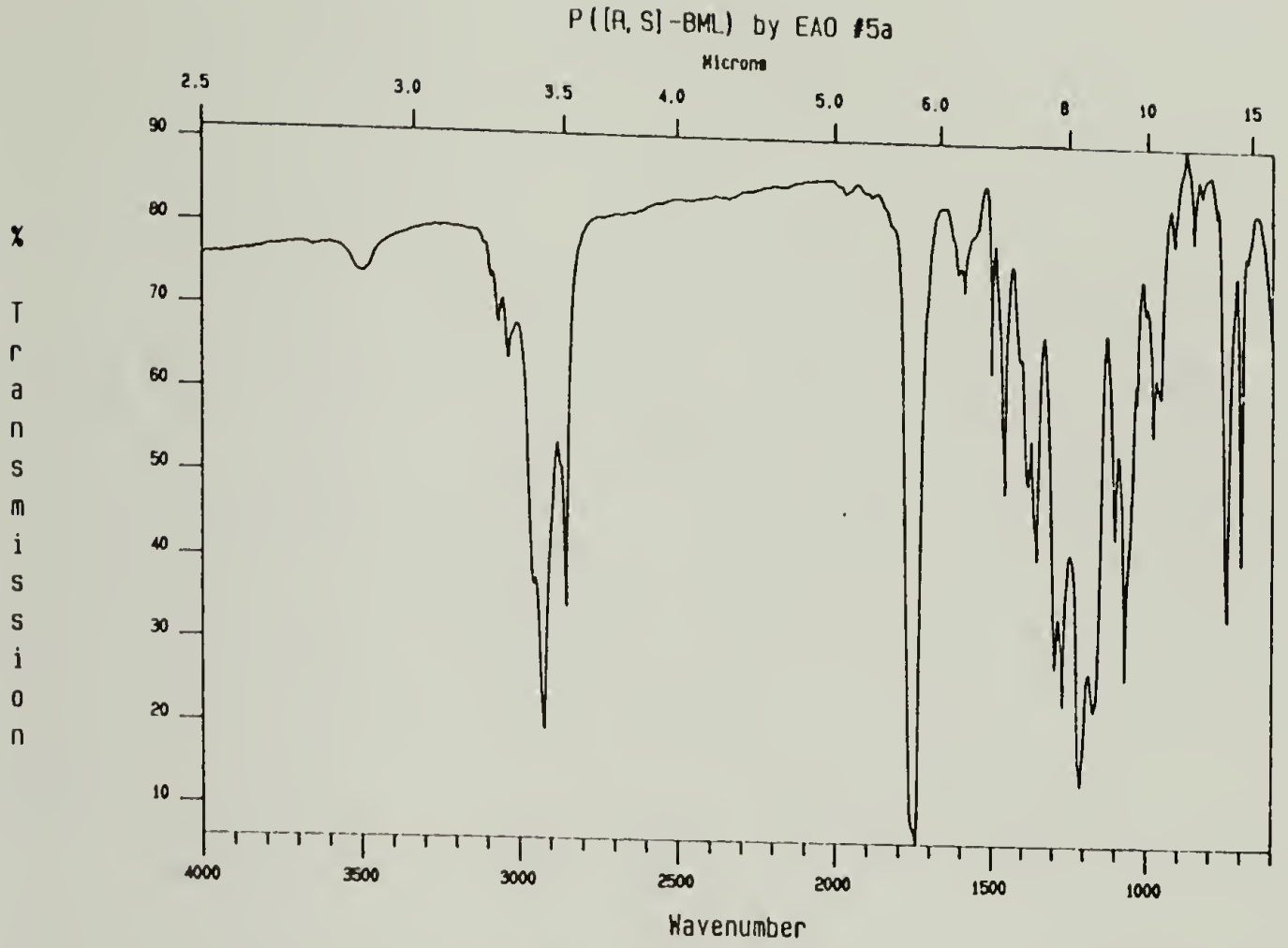
IR Spectrum No. 6 BENZYL [R]-O-MESYLBUTYRATE



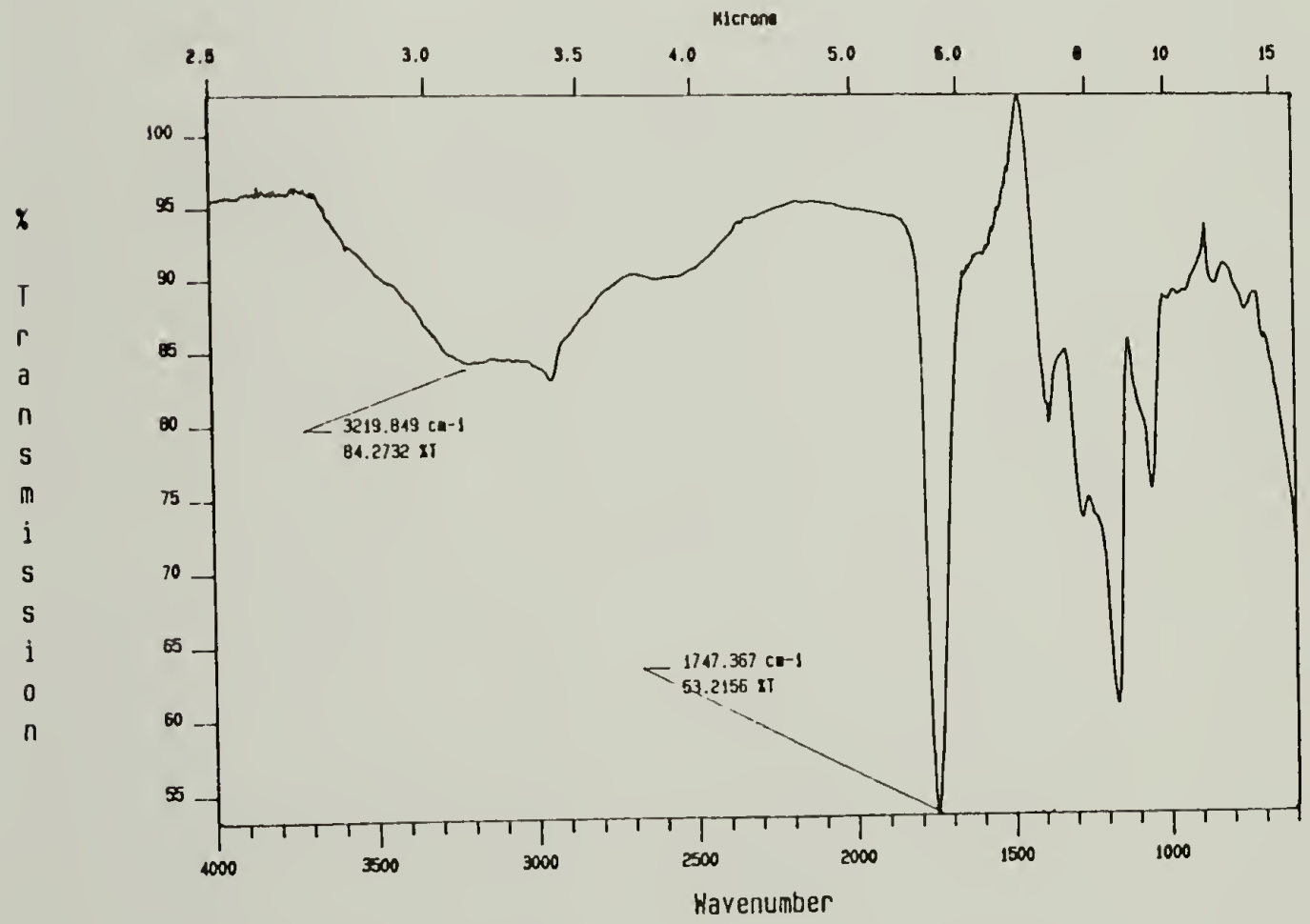
IR Spectrum No. 7 [R]-O-MESYLBUTYRIC ACID



IR Spectrum No. 8 [S]-β-BUTYROLACTONE



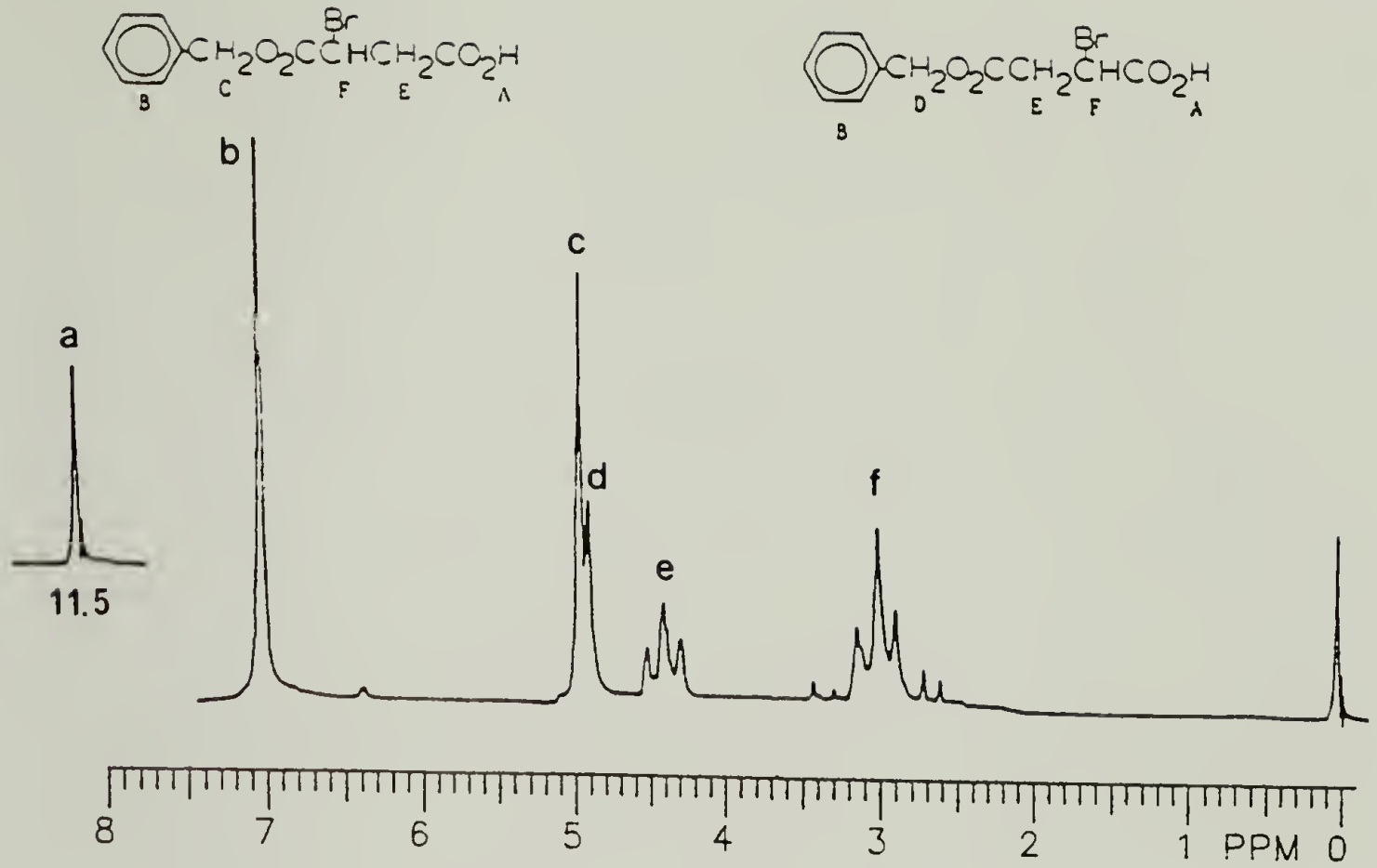
FTIR Spectrum No. 9 P([R,S]-BML) SYNTHESIZED BY EAO



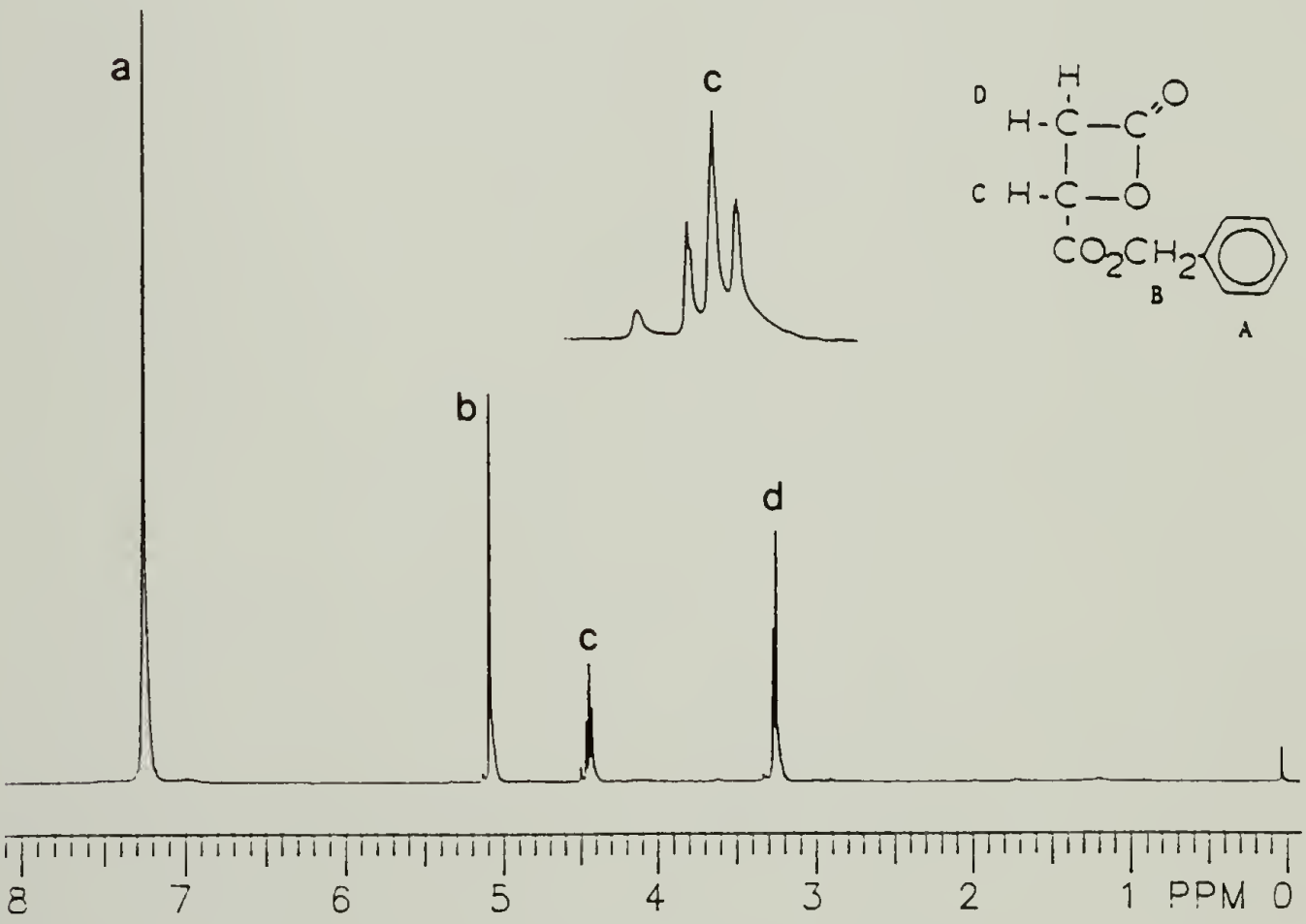
FTIR Spectrum No. 10 POLY(MALIC ACID) (PMA)

APPENDICES B

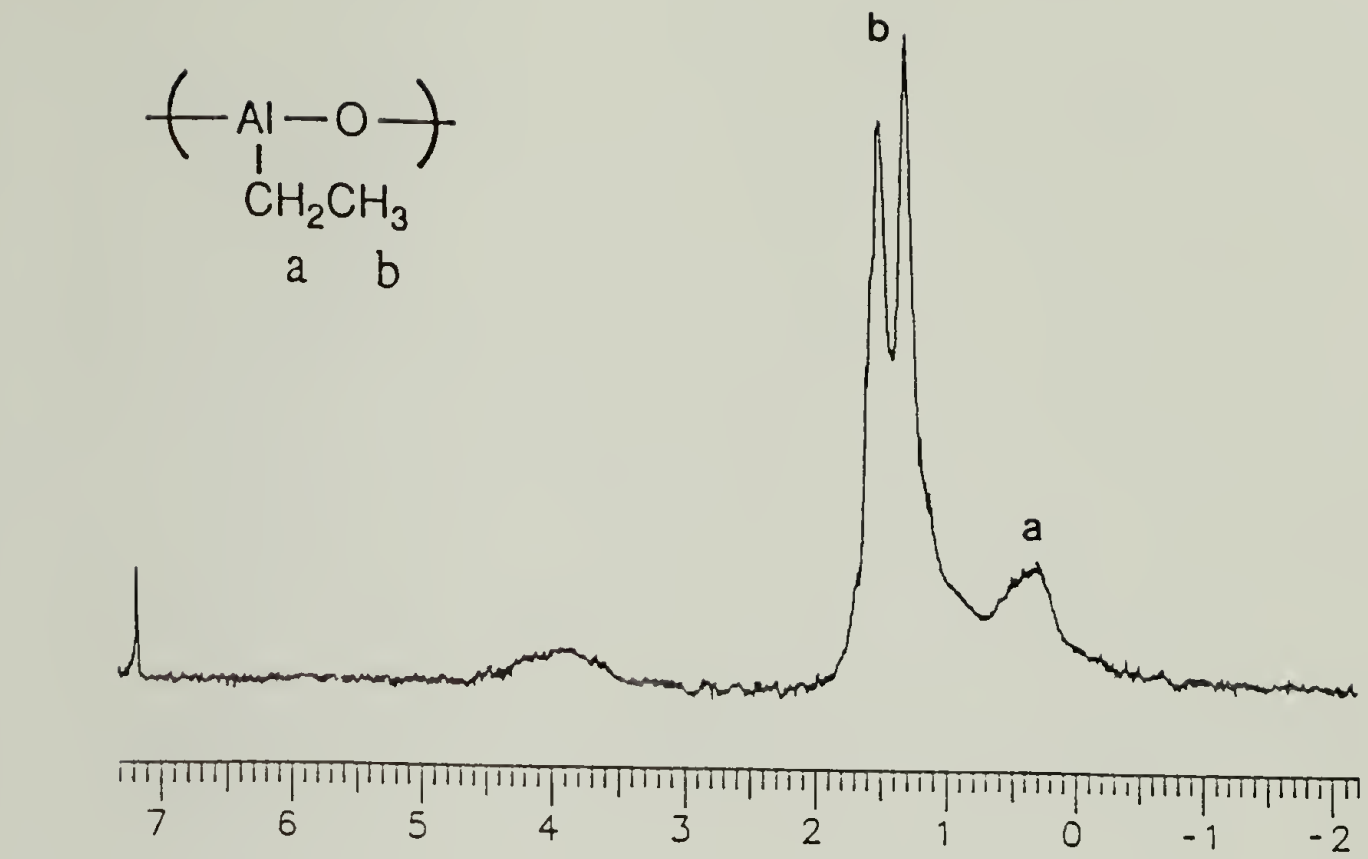
PROTON NMR SPECTRA



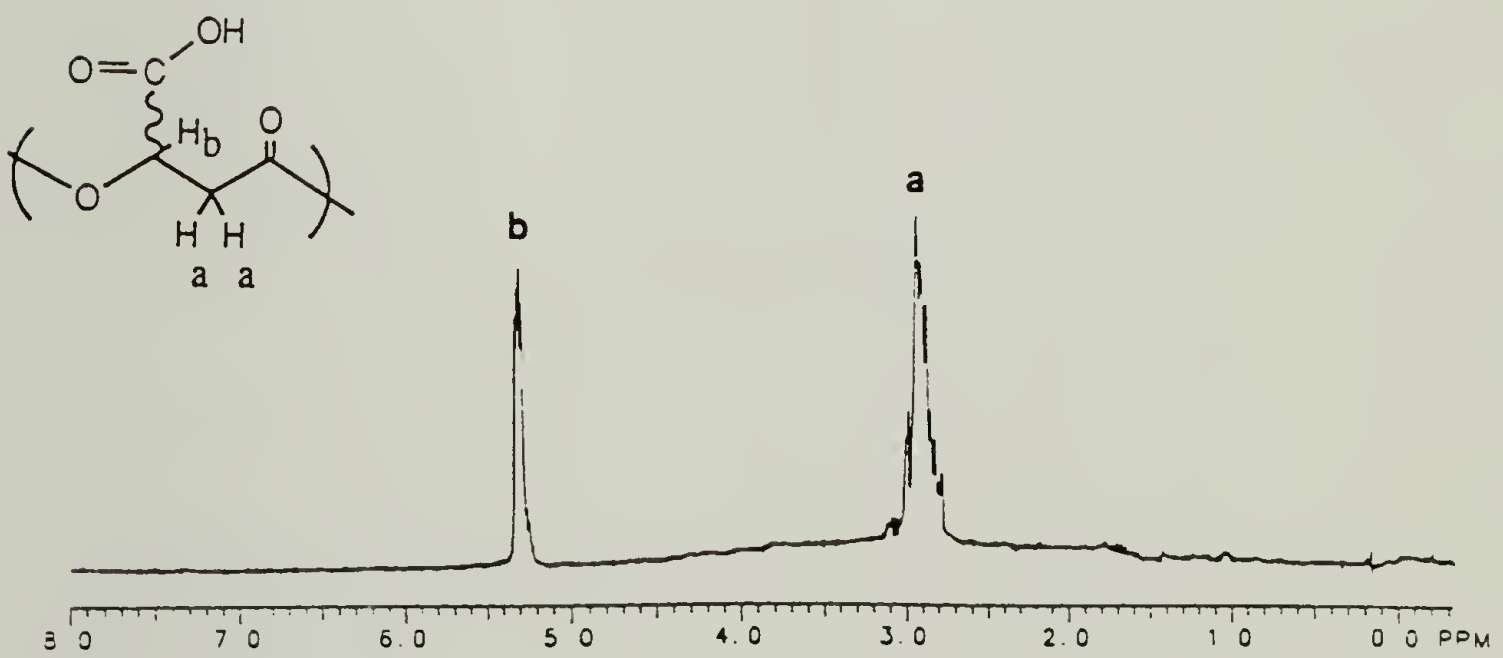
^{1}H-NMR Spectrum No. 1 BENZYL BROMOSUCCINATE(S)



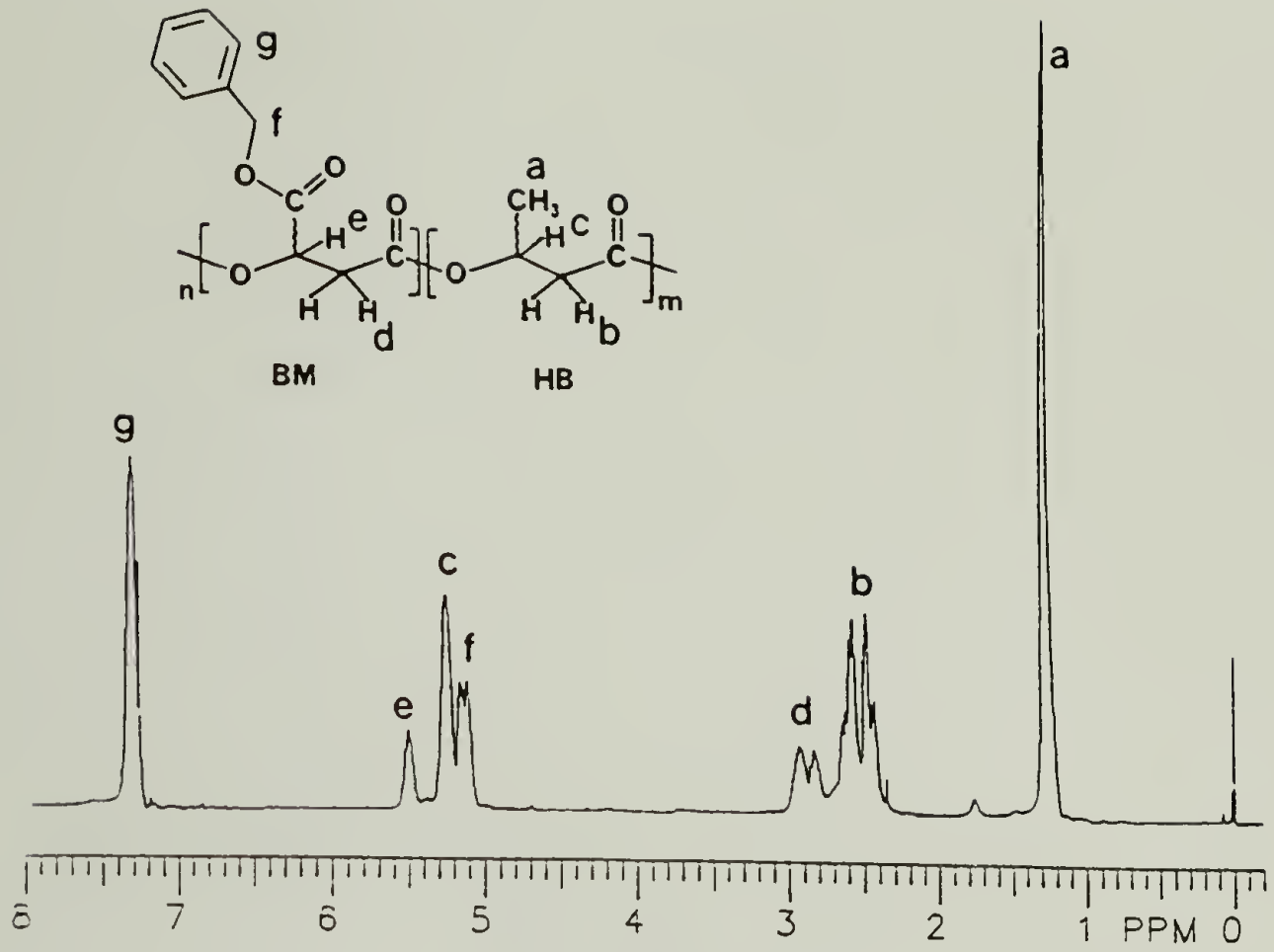
^{1}H-NMR Spectrum No. 2 BENZYL BUTYROLACTONE



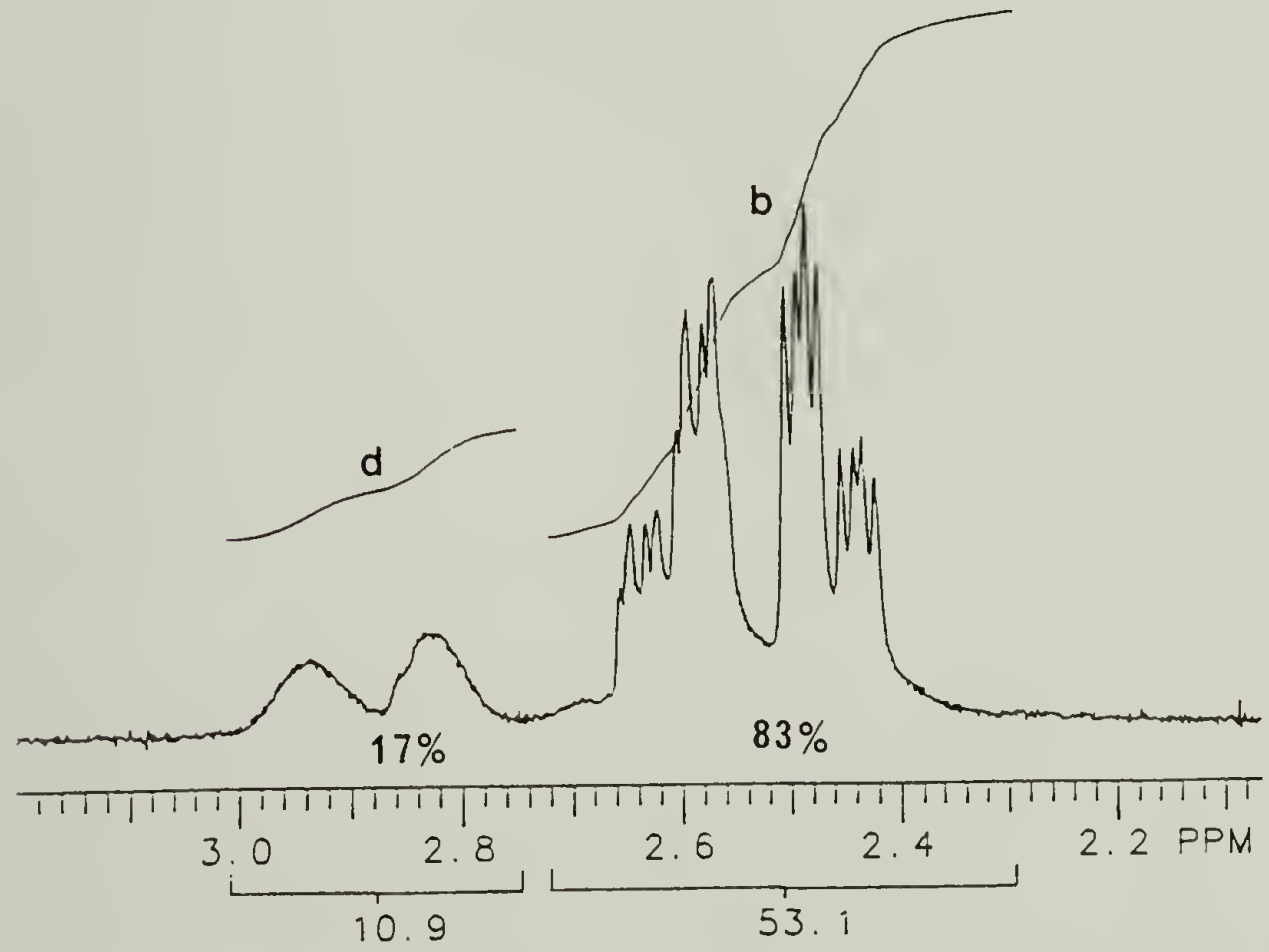
^{1}H-NMR Spectrum No. 3 ETHYL ALUMINOXANE (EAO)



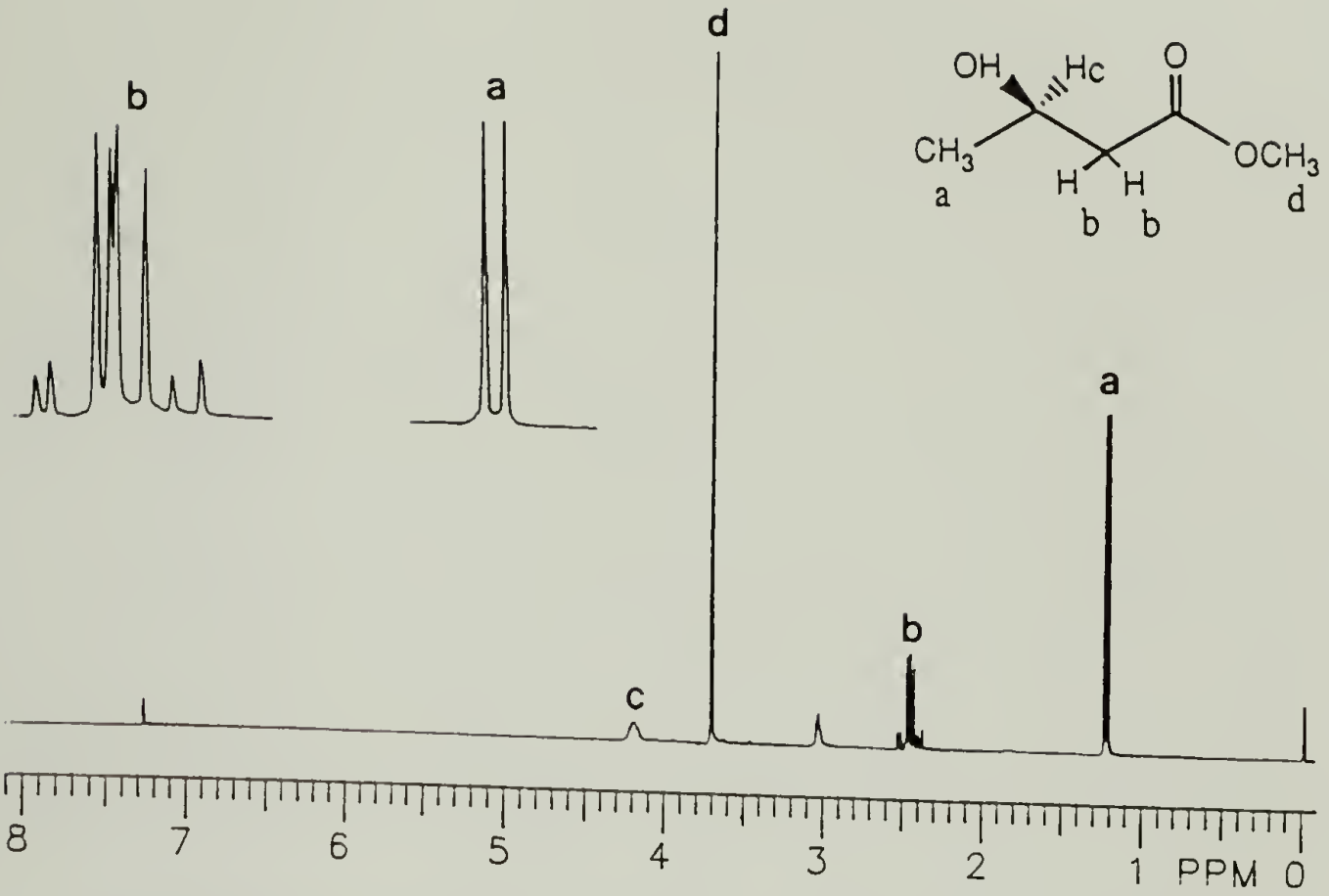
^{1}H-NMR Spectrum No. 4 POLY(MALIC ACID) (PMA)



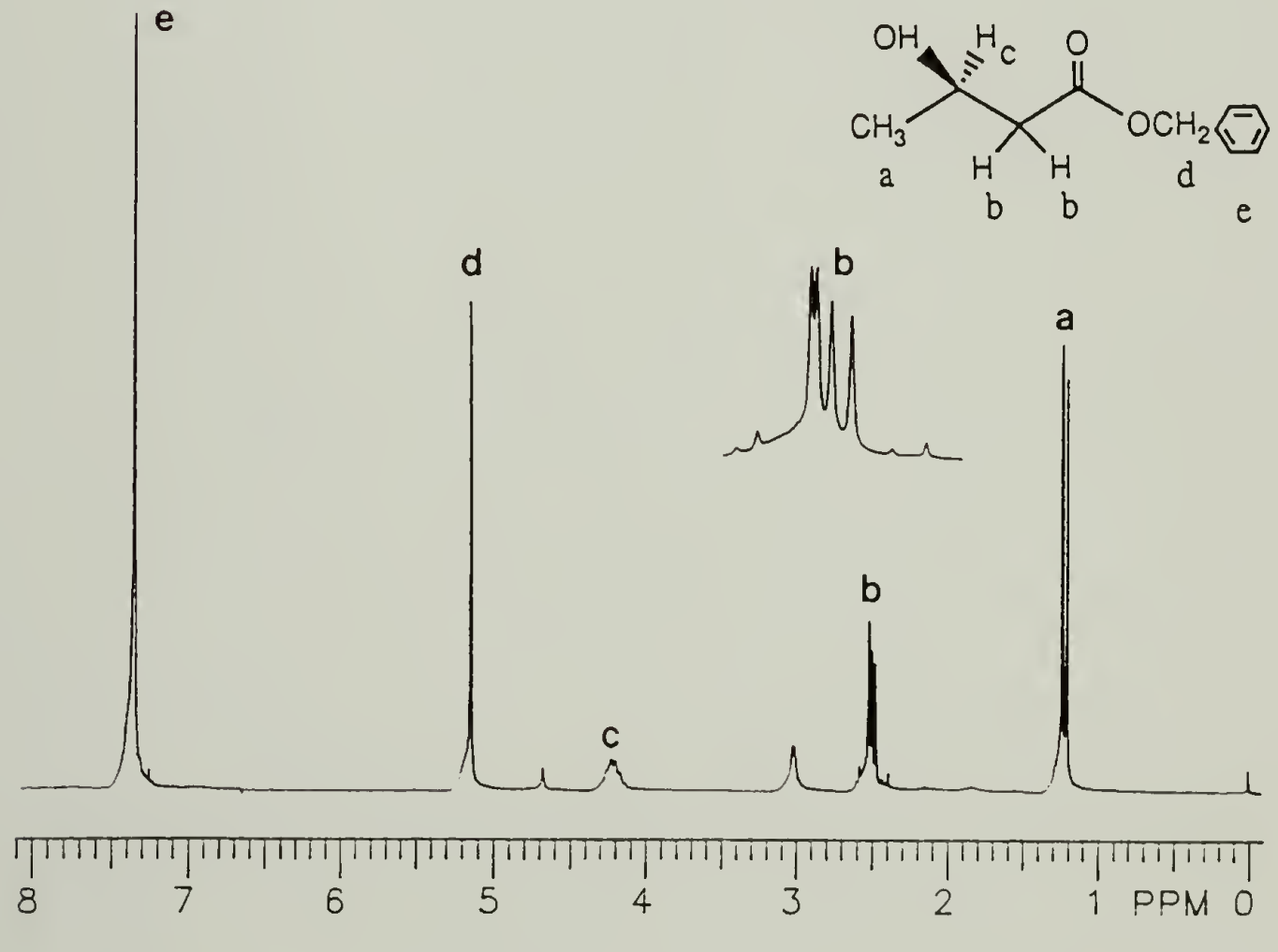
^{1}H-NMR Spectrum No. 5 P(HB-co-BM) (70:30)



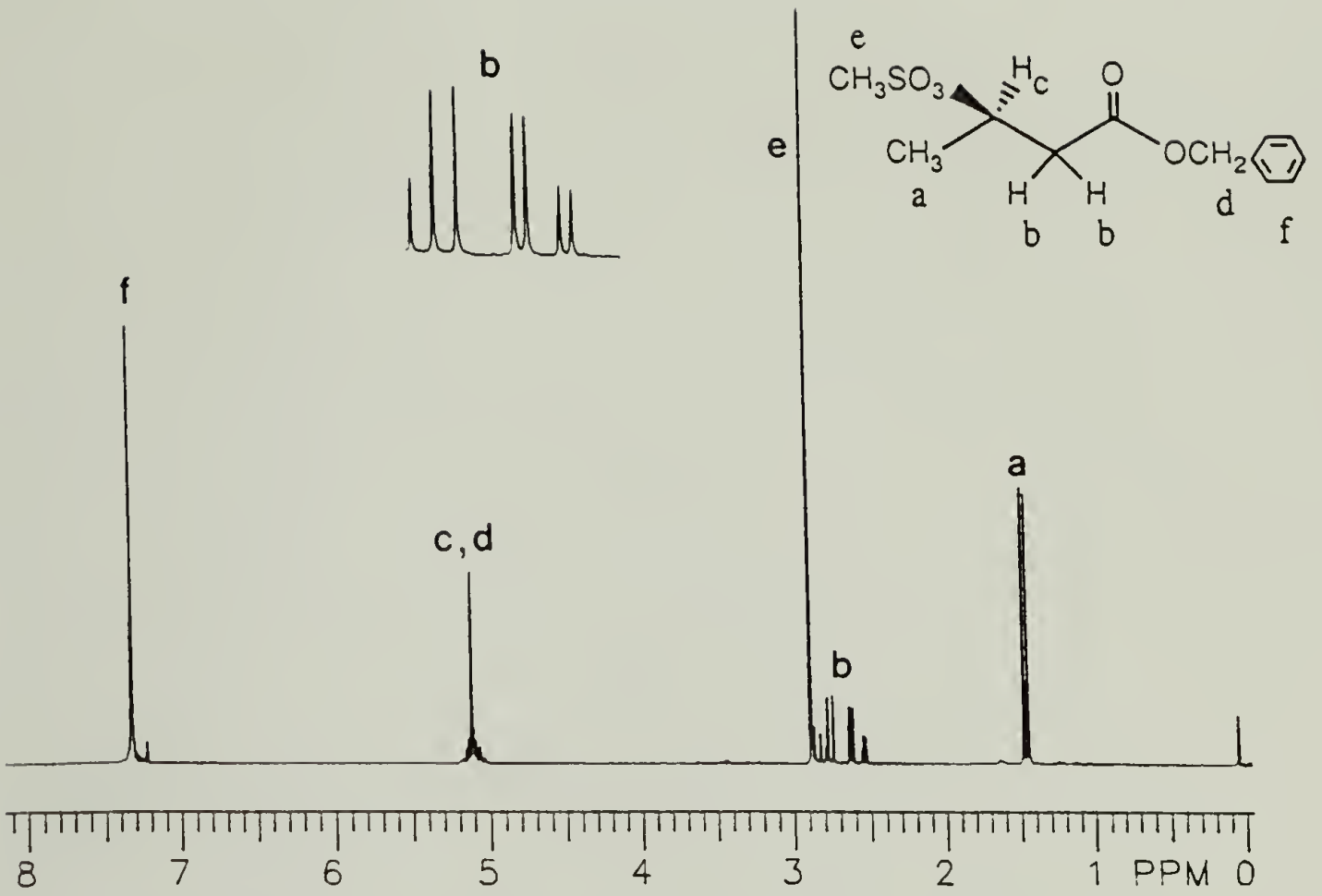
^{1}H-NMR Spectrum No. 6 EXPANSION OF METHYLENE PROTONS OF P(HB-co-BM) (80:20)



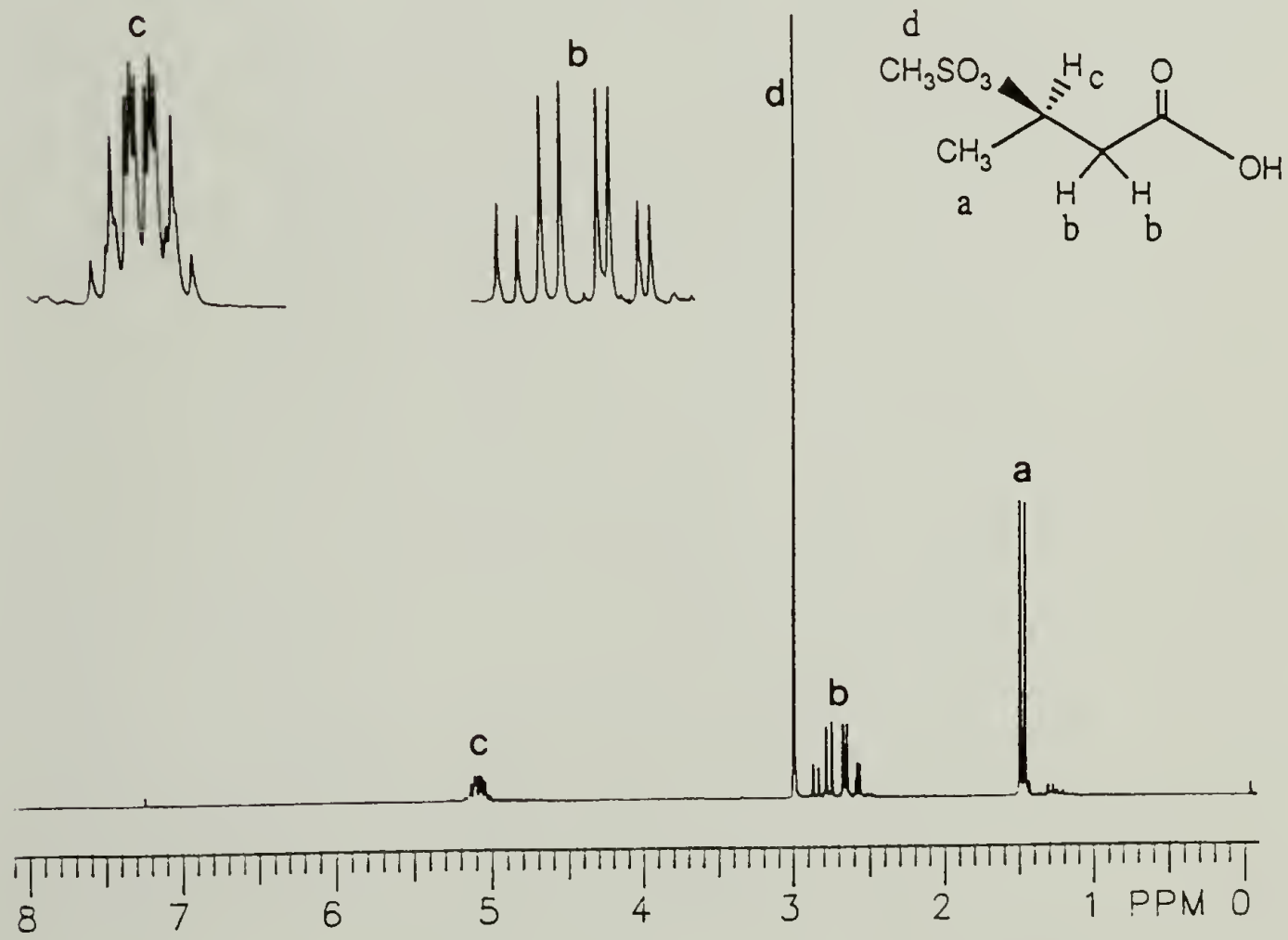
¹H-NMR Spectrum No. 7 METHYL-[R]-β-HYDROXYBUTYRATE



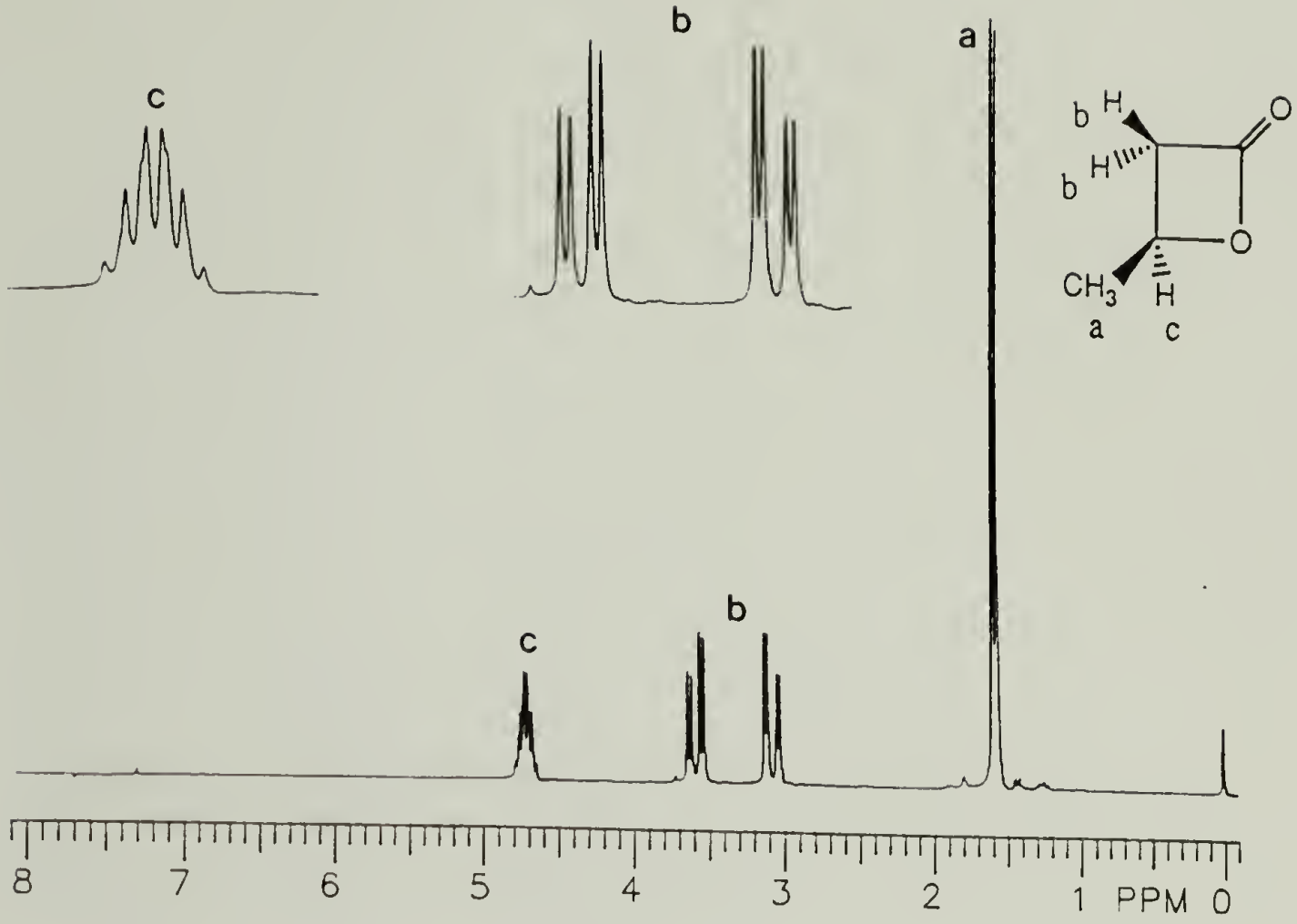
¹H-NMR Spectrum No. 8 BENZYL [R]-β-HYDROXYBUTYRATE



¹H-NMR Spectrum No. 9 BENZYL [R]-O-MESYLBUTYRATE



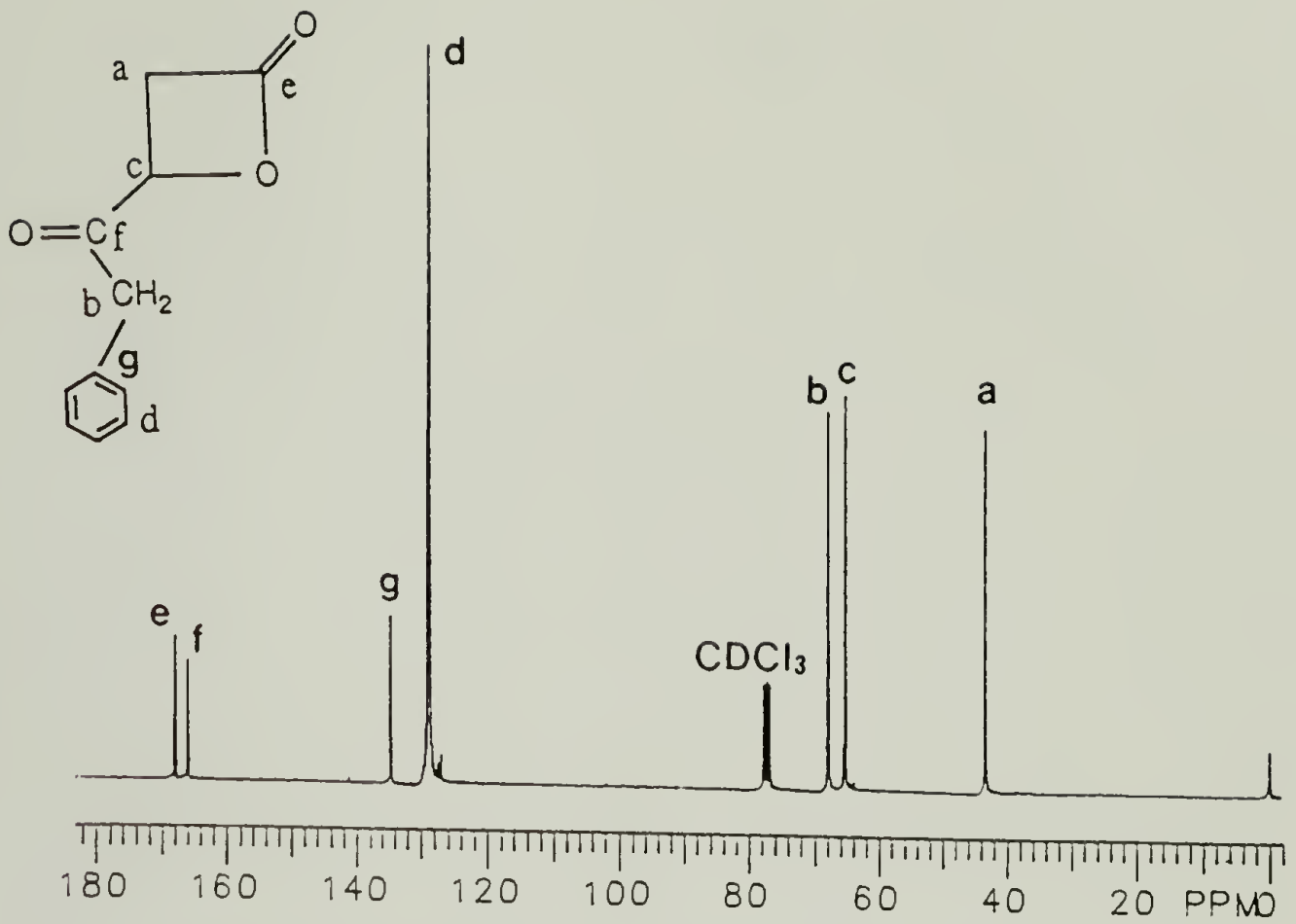
¹H-NMR Spectrum No. 10 [R]-O-MESYLBUTYRIC ACID



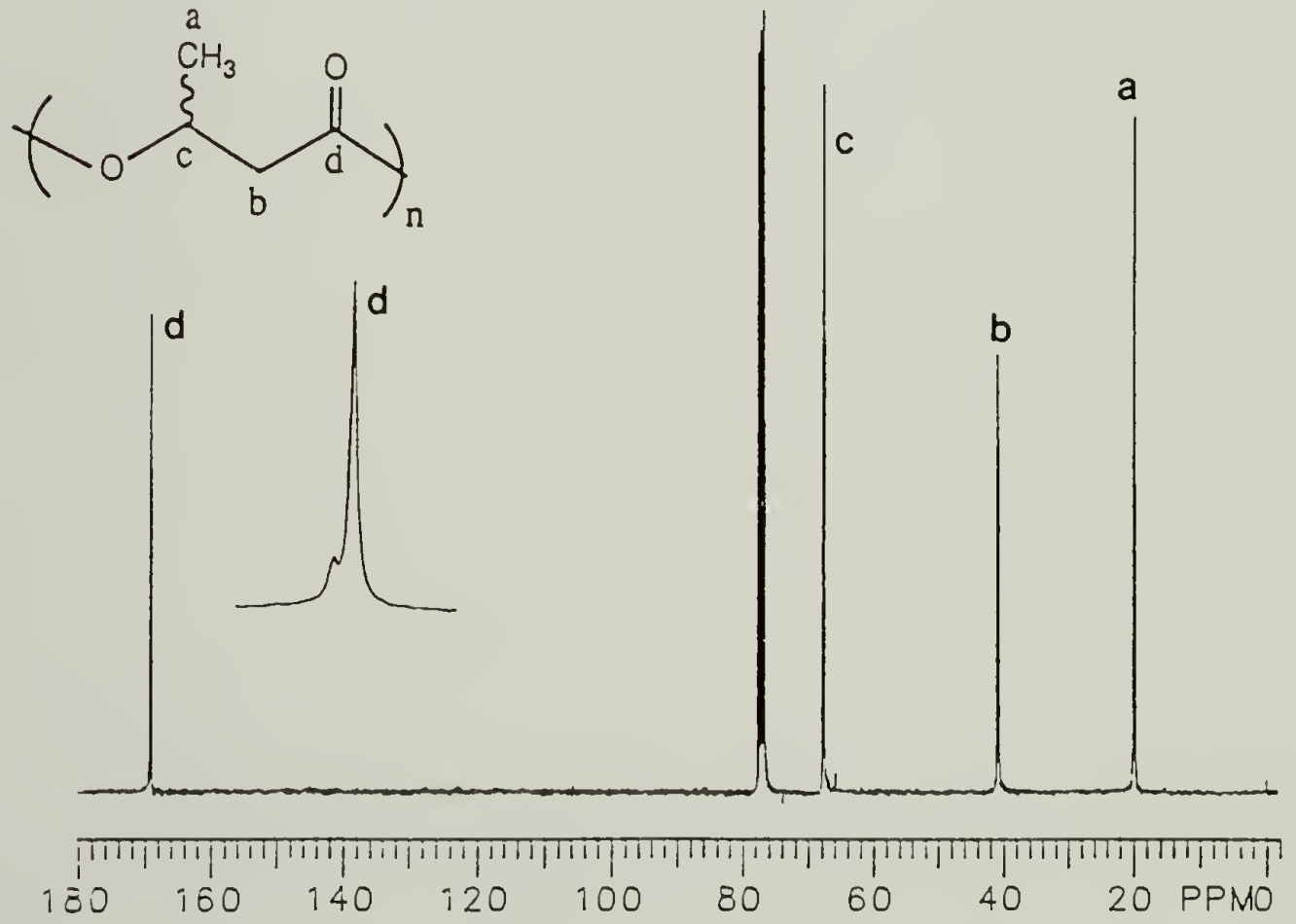
^{1}H-NMR Spectrum No. 11 [S]-β-BUTYROLACTONE

APPENDICES C

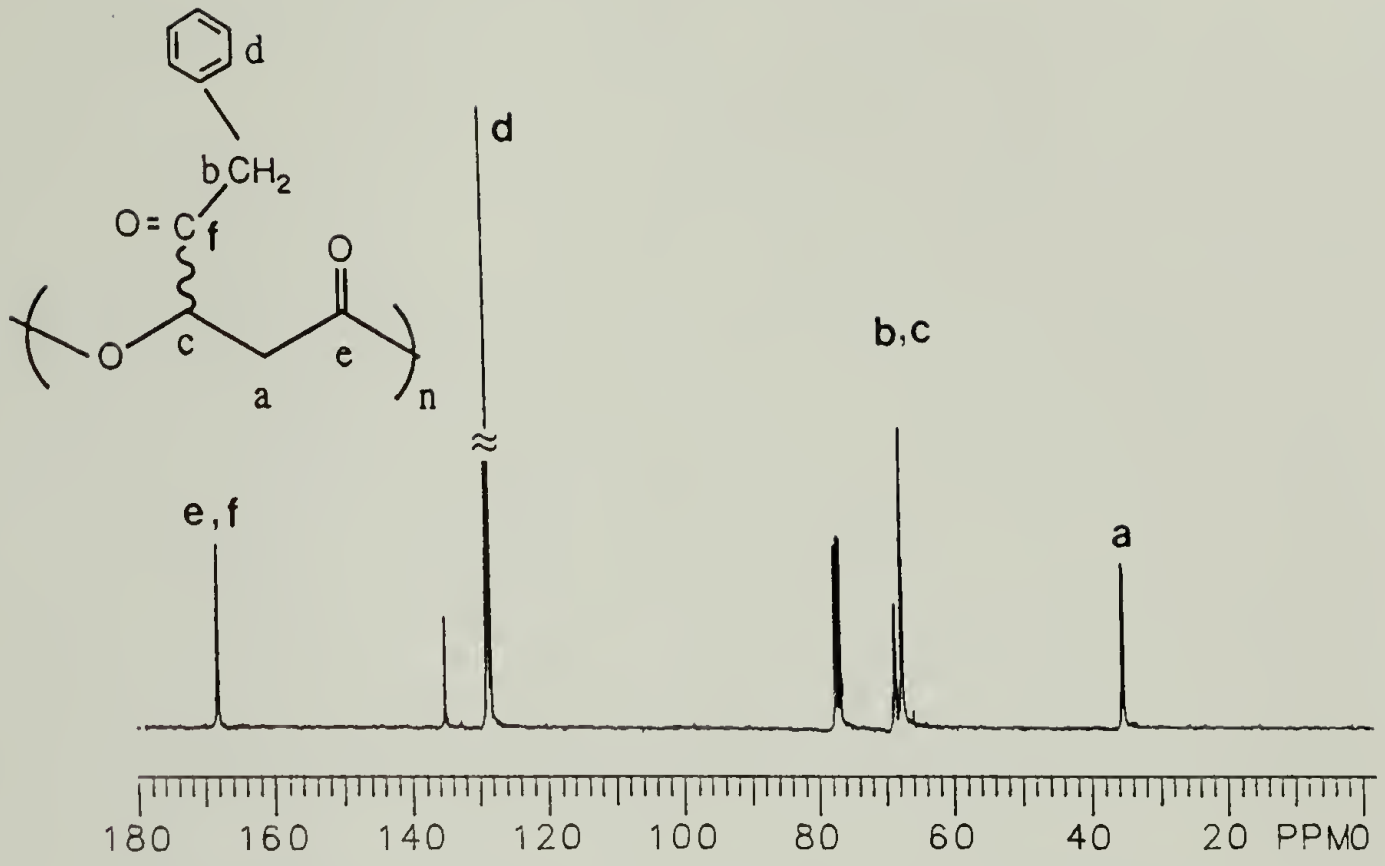
CARBON-13 NMR SPECTRA



^{13}C-NMR Spectrum No. 1 BENZYL MALOLACTONE



^{13}C-NMR Spectrum No. 2 P([R,S]-HB) SYNTHESIZED BY EAO



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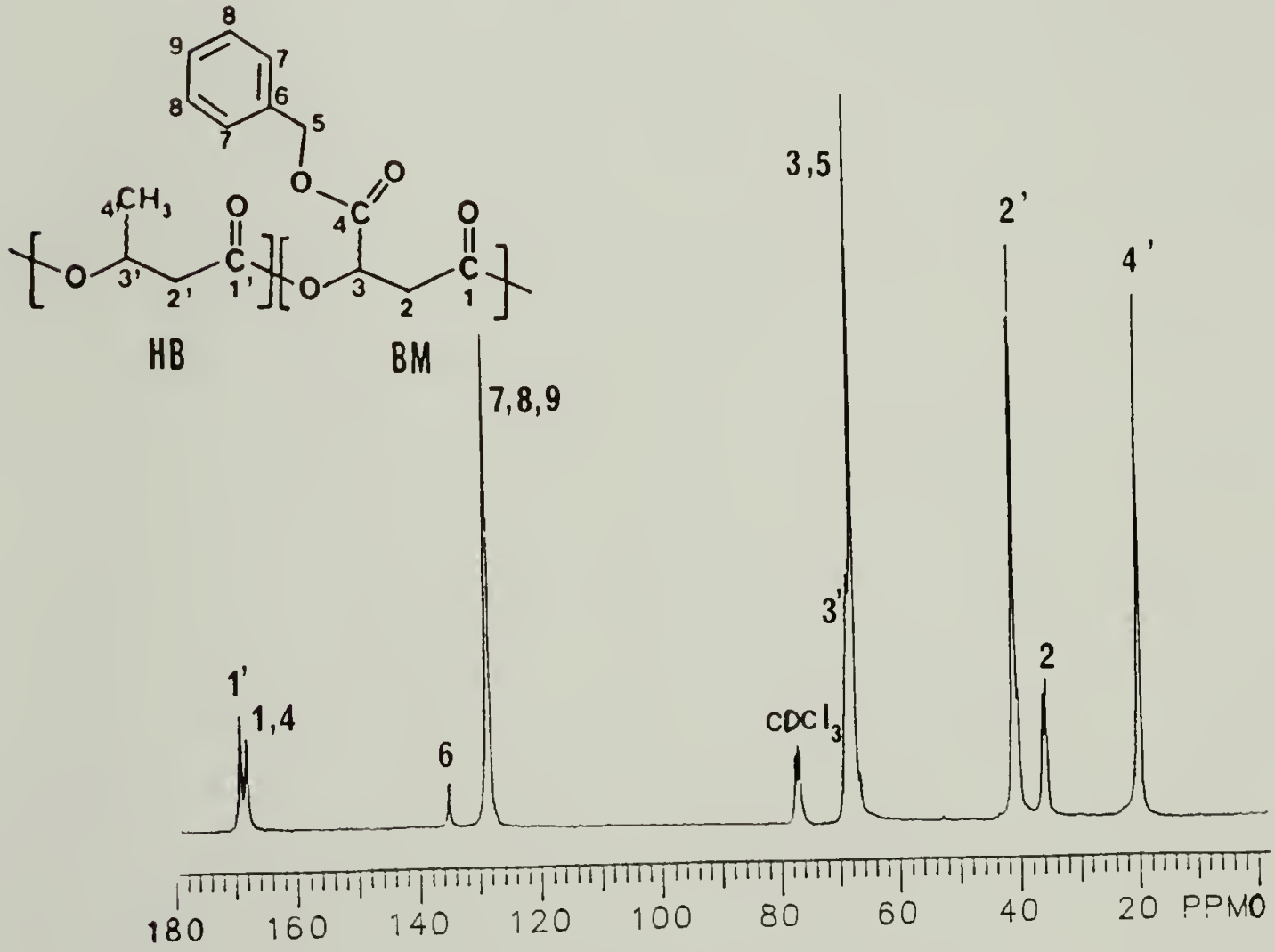
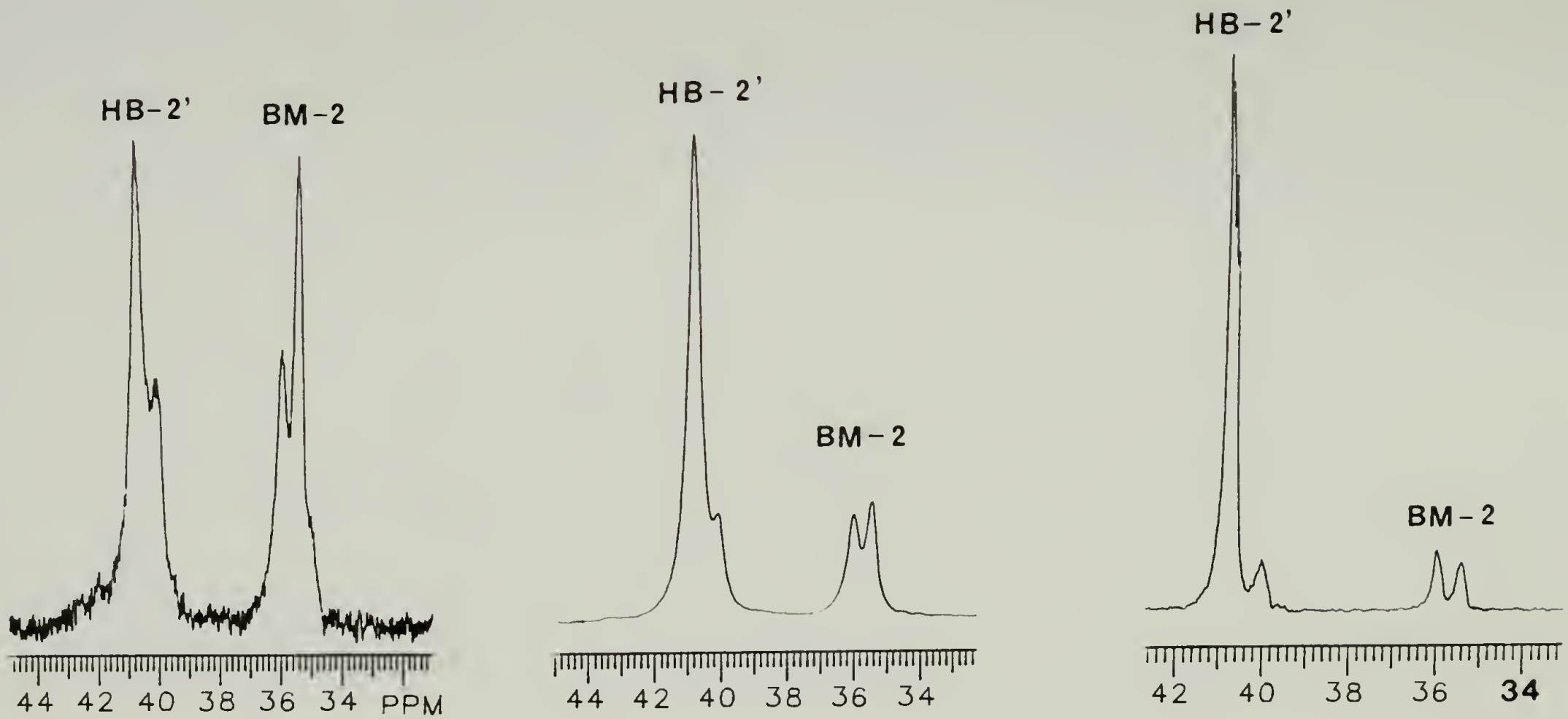


^{13}C-NMR Spectrum No. 4 P(HB-co-BM) (70:30)



HB:BM = 50:50 　　70 : 30 　　80 : 20

^{13}C-NMR Spectrum No. 5 EXPANSIONS OF METHYLENE CARBON OF P(HB-co-BM)

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