Compositional Analysis of Biodegradable Polyphosphoester Copolymers Using NMR Spectroscopic Methods

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ABSTRACT: The chemical composition and quantitative molar ratios among all components of biodegradable polyphosphoester copolymers of DL-lactide and ethylphosphate were determined by a comprehensive set of NMR spectroscopic methods. The polyphosphoester copolymers studied were synthesized using condensation polymerization of oligomeric DL-lactide prepolymers and ethyl dichlorophosphate. Conclusive identification of the chemical shift patterns of all functional groups in the copolymers required additional NMR methods such as ^{31}P-NMR and two-dimensional ^{1}H–^{1}H COSY NMR, in addition to the synthesis and comparative NMR analysis of model compounds possessing identical phosphoester linkages in the polyphosphoester copolymers. For the polymers synthesized using the bulk polycondensation process, ^{1}H–^{1}H COSY NMR analysis revealed the presence of a small amount of side products that were undetected by ^{1}H-NMR alone. These side reactions most likely occurred between the pendant ethoxy group of the phosphoesters and the hydrogen chloride gas generated in the bulk polycondensation process. ^{31}P-NMR spectra of the copolymers revealed a consistent triple-peak pattern characteristic of phosphoesters linked to a racemic mixture of D,L-lactides. These results offered new insight into the side reactions occurring in bulk polymerization of polyphosphoesters and provided a powerful tool of characterizing complex biodegradable polymers. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 90: 4021–4031, 2003

Key words: NMR; polyphosphoesters; controlled release; drug delivery; biodegradable polymers

INTRODUCTION

Polyphosphoesters are a relatively new family of biodegradable polymers that are being actively investigated for pharmaceutical and biomedical applications such as drug delivery and tissue engineering.[1–3] The performance of these polymers for biomedical applications largely depends on their high purity and consistent molecular weight. A number of synthetic routes have been explored for the synthesis of these polymers, with the intention of obtaining high molecular weight. Some of the processes examined include ring-opening,[1] bulk polymerization,[2] and enzymatic polymerization.[4] Although the merits and drawbacks of these processes have been studied with regard to polymer molecular weight, the purity of the final polymers and side reactions occurring during the process have seldom been specifically evaluated. Bulk polycondensation is often used as a preferred route for large-scale production of high molecular weight polymers because of its apparent advantages such as short reaction times, minimal purification steps, and feasibility for scale-up. Various researchers have used this approach to produce linear high molecular weight polyphosphates.[5,6] It has been noted, however, that bulk polymerization requires a high temperature to melt all the reactants and frequently leads to side products that limit the molecular weight and increase the polydispersity (PD) of the final polymer.[7] Such side reactions are especially not desirable in biomedical applications, wherein polymers with high purity and well-characterized chemical structures are both desired and required. In this study we aim to compare the reaction conditions of two synthesis processes, solution polymerization and bulk polycondensation, and evaluate their respective ability in producing a novel poly(phosphoester) copolymer of DL-lactide and ethylphosphate, We also aim to use NMR methods to evaluate the occurrence and extent of potential side reactions during the two types of polymerizations. Specifically, proton (^{1}H), phosphorus (^{31}P), and COrelational SpectrocopY (COSY) NMR spectroscopic techniques were extensively used to characterize the identity and purity of the polymers produced using the two processes. We also synthesized a series of analog compounds that contained the same ethylphosphate linkages in the polymers for a conclusive assignment of chemical shifts on ^{1}H-NMR and the elucidation of a unique triple-peak pattern of ^{31}P-NMR of the copolymers. Our final aim is to use NMR spectroscopy to support gel permeation chromatography (GPC) as an

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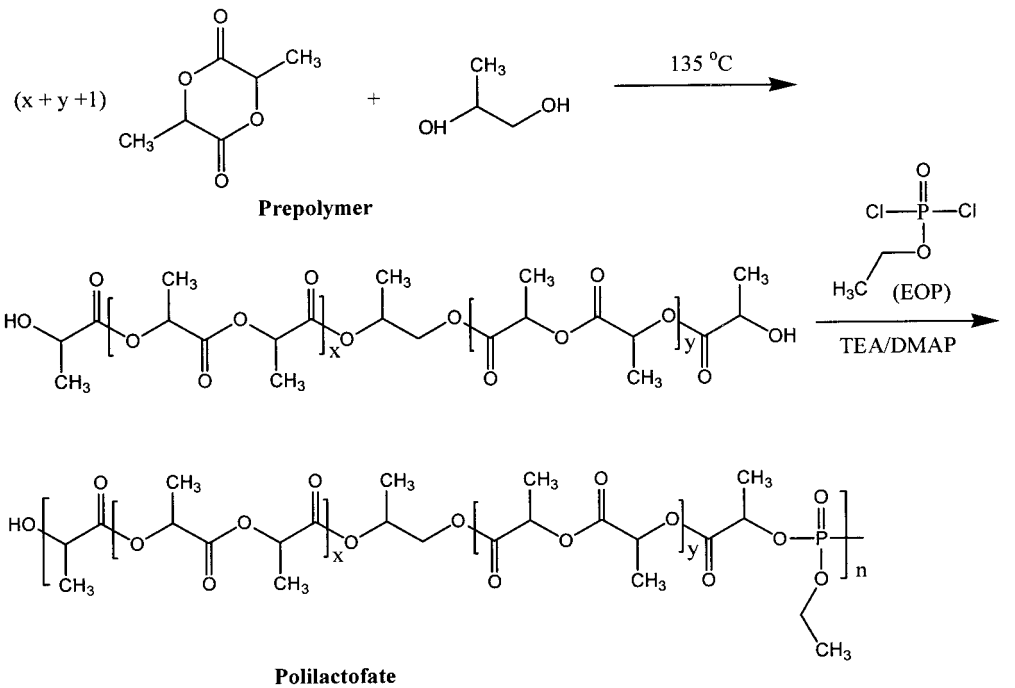

Figure 1 Synthetic scheme for polilactofates. The second step does not involve catalysts in the bulk polycondensation approach, whereas catalysts listed are used for solution polymerization.

alternate method for an accurate determination of the polymer molecular weight (M_n).

The biodegradable polyphosphoester examined in this study, polilactofate, is a copolymer consisting of DL-lactide and ethyl phosphate. Polilactofate synthesized using solution polymerization process is currently being tested in clinical trials as a drug carrier for the sustained delivery of a chemotherapeutic agent, paclitaxel,[8] and a local anesthetic agent lidocaine.[9] The general structure and reaction scheme of the polymer are depicted in Figure 1. The two-step synthesis of the polymer is described elsewhere in detail.[10] Briefly, the first step involves the ring-opening polymerization of DL-lactide, initiated by propylene glycol (PG), with stannous octoate [$Sn(Oct)_2$] as the catalyst, to form the lactide prepolymer. In the second step, the lactide prepolymer is reacted with ethyl dichlorophosphate to form the final copolymer. The first step is prone to transesterification reactions, which are commonly seen in polycondensation of lactide polymers. Specific side reactions occurring during the second step are likely to be restricted to the polymer side chains. The byproducts formed in such reactions are consequently difficult to separate, given the fact that the majority of the polymers remain unchanged. Thus novel direct as well as indirect approaches are needed to estimate the actual composition of the final polymers, to assess the type and extent of the side reactions, and to design suitable processes to eliminate such undesired reactions.

Characterization of the polymers and byproducts was done using one-dimensional ^{1}H- and ^{31}P-NMR, and two-dimensional ^{1}H–^{1}H COSY NMR methods. Model compounds as well as computer simulations were used to assist in peak assignment of the final polymer. Although NMR has been used extensively for polymer characterization in the past,[11,12] only limited examples exist in which a combination of NMR methods such as COSY NMR and synthesis of a model compound are used to characterize newly created biomedical polymers. Kohn and coworkers[13] used model compounds to mimic the repeating polymer structure to gain insights into the polymer degradation mechanism. Allcock and coworkers[14] used model compounds to understand the effect of gamma irradiation on the structure of a new class of polyphosphazenes. The need for model compound studies for the polilactofates stemmed primarily from the pentavalent nature of phosphoesters and the different reactivity associated with the three phosphoester bonds. The unique nature of these phosphoester linkages may give rise to a multitude of possible side reactions that may occur during polymerization if appropriate process conditions are not chosen. The complexities associated with phosphate were effectively elucidated by the use of two-dimensional ^{1}H–^{1}H COSY NMR. In recent years COSY NMR has been successfully used for the spectral characterization of novel biodegradable polymers with complex chemical linkages.[15,16] Such a two-dimensional NMR technique is very effec-

tive in determining the correlations between different groups in the polymer. Finally, COSY NMR also offers the ability to determine whether any unexpected correlations or linkages may exist in the polymer and display any peak that may be hidden under or overlapped with other larger peaks and thus invisible on a regular ^{1}H-NMR spectrum. This particular aspect makes COSY NMR very powerful in identifying any potential side products formed during a polymerization process.

EXPERIMENTAL

Materials

DL-Lactide was purchased from Purac America (Lincolnshire, IL) and was dried in a desiccator under vacuum for at least 2 days. Propylene glycol and 4-dimethylaminopyridine (DMAP; ACS reagent grade, purity 99.5%), and *R*- and *S*-methyl lactate (purity $>$ 97%) were purchased from Aldrich (Milwaukee, WI) and used without further purification. Ethyl dichlorophosphate (EDP) and triethylamine (TEA) were purchased from Aldrich and were vacuum distilled before use. Purity of the distilled EDP fractions was determined by gas chromatography and fractions $>$ 99% pure were combined and used for polymerization. Stannous octoate (purity $\sim$ 90%) was bought from Pfaltz and Bauer (Waterbury, CT) and used without further purification. All solvents were of ACS anhydrous reagent from Aldrich and used without purification.

Molecular weight determination

Weight-average and number-average molecular weights (M_w and M_n, respectively) and polydispersity (M_w/M_n) of the prepolymers and polymers were determined using a Waters GPC system equipped with a Model 515 pump, a 717plus Autosampler, and a Model 410 differential refractometer (Waters Chromatography Division/Millipore, Milford, MA). The samples were prepared in dichloromethane (DCM) at a concentration of 5–10 mg/mL and the injection volume was 100 μL. A PLgel mixed-C 5-μm column (dimensions 300 $\times$ 7.5 mm; Polymer Laboratories, Amherst, MA) was used for the separation. Polymer samples were eluted in DCM at the rate of 1 mL/min and the molecular weight was determined relative to the polystyrene standards obtained from Polymer Laboratories.

NMR characterization

NMR spectra were acquired on a 400-MHz Bruker NMR spectrometer (Model 400-Spectrospin; Bruker Instruments, Billerica, MA). Samples were prepared in chloroform-d containing 0.03% TMS as an internal standard. Sample concentrations of about 20–30 mg/mL were used for ^{1}H- and ^{31}P-NMR, and 100 mg/mL for ^{13}C-NMR, respectively. Computer simulations for NMR spectra were performed using ACD NMR Predictor Version 5.09 Simulation Software (ACD Labs, Ontario, Canada).

Synthesis of copolymers of lactide and ethylphosphate

The lactide–phosphate copolymer was synthesized in two steps as shown in Figure 1. In the first step, a lactide prepolymer was prepared by a ring-opening polymerization of DL-lactide, using PG as the initiator and $Sn(Oct)_2$ as the catalyst. Unreacted lactide was removed by application of a vacuum at 125°C for 2 h.

For the bulk polymerization process, the polymerization between lactide prepolymer and ethyl dichlorophosphate (EDP) was achieved at a high temperature (125–135°C) with a continuous nitrogen purge. The removal of hydrogen chloride gas (HCl) evolved during the reaction was facilitated by applying a weak vacuum.[2] For the solution polymerization approach, the lactide prepolymer was reacted with EDP at a low temperature (-10 to -15°C) in a solvent such as chloroform with TEA and DMAP as acid acceptor and catalyst, respectively. At the end of the reaction, the reaction solvent was removed using a rotary evaporator and the polymer mass was dissolved in acetone. The insoluble salts were filtered out and the residual base and catalyst were subsequently removed using a combination of acidic and neutral ion-exchange resins. The final polymers made by both processes were dissolved in dichloromethane and precipitated in a mixed solvent system of petroleum ether : ethyl ether (3 : 1, v/v), followed by drying in a vacuum oven to constant weight. The resulting copolymers were white amorphous solid soluble in common organic solvents such as acetone, chloroform, and dichloromethane.

Synthesis of model compounds

As shown in Figure 2, bis(methoxylactidyl) ethylphosphate (BMLEP) was synthesized by reacting EDP and methyl lactate in a 1 : 2 ratio in DCM, with TEA (2.25 parts) and DMAP (0.25 parts) as acid acceptor and catalyst, respectively. The remaining base and catalyst were removed by ion-exchange resins and the final compound was purified by flash chromatography.

RESULTS AND DISCUSSION

^{1}H-NMR analysis of lactide prepolymers

Ring-opening polymerization of lactides has been extensively studied and was used in our study for the

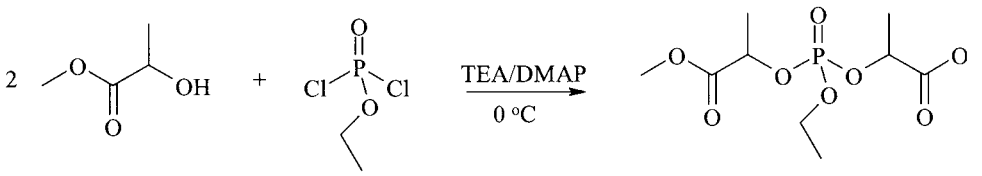

Figure 2 Synthetic scheme for bis(methoxylactidyl) ethylphosphate (BMLEP).

synthesis of lactide prepolymers. PG was added quantitatively as an initiator to open the lactide and create dihydroxyl end-capped lactide prepolymers with controlled molecular weight. ^{1}H-NMR and ^{1}H–^{1}H COSY NMR spectra for the prepolymer are shown in Figure 3(a) and (b), respectively. The assignment of the chemical shifts for different groups was done based on the NMR spectra of the reactants, DL-lactide and PG, correlations between functional groups obtained from COSY NMR, and typical NMR spectra of lactide-based telechelic prepolymers reported in the literature.[17] Of particular interest were the chemical shifts of the methylene proton (C**H**$_2$) and methine proton (C**H**) in PG, which changed substantially after incorporation in the prepolymers. COSY was particularly helpful in differentiating peaks that are overlapping with each other. For example, as shown in Figure 3(b), the correlations marked as L and G could be used for an accurate identification of PG peaks. COSY analysis of the prepolymer revealed that methylene H and methine H of PG shifted to about 4.2 and 5.1 ppm from 3.5 and 4.2 ppm, respectively. The latter overlapped with that of the methine H of lactide (5.1 ppm) in the middle of the polymer chains. Based on the NMR analysis, it could be seen that PG as the initiator was completely incorporated in the prepolymer at the end of the reaction. No peak was observed on ^{1}H-NMR to indicate the presence of PG in the unreacted form or at any polymer chain ends. This suggests that despite the asymmetric nature of PG, the initial reaction between the primary hydroxyl group of PG and the lactide effectively generated an intermediate with two secondary diol end groups. Subsequent reactions occurred at both ends resulting in a telechelic lactide prepolymer. In addition, the ratio of lactide to propylene glycol estimated based on NMR peak integral values matched the feed ratio of the starting materials, indicating a near-complete conversion of lactide into the prepolymer. Unreacted monomers were removed by sublimation at high temperature and under vacuum.

^{1}H-NMR assignment of polilactofate made by solution polymerization

Based on the reaction scheme, it appears that ^{1}H-NMR spectra of the polymer should be similar to those of the lactide prepolymer, except for additional peaks representing ethyl phosphate linkages. The methyl H of ethylphosphate appeared as a new peak at 1.36 ppm, next to that of PG. The methylene H of ethylphosphate shifted to about 4.3 ppm, overlapping substantially with that of PG and the methine H of lactide located at the end of the polymer chains. To conclusively assign all the peaks of ethylphosphate and lactide groups attached to the phosphoester linkages, a ^{1}H-NMR spectrum of a model compound, BMLEP, was acquired and used as reference. The structure and ^{1}H-NMR spectrum for BMLEP are shown in Figure 4. Chemical shifts of BMLEP were assigned as follows: 1.36 ppm for $POCH_2C\mathbf{H}_3$, 1.58 ppm for $POCH(C\mathbf{H}_3)COOCH_3$, 4.22 ppm for $POC\mathbf{H}_2CH_3$, 4.85–5.0 ppm for $POC\mathbf{H}(CH_3)COOCH_3$. Given a small molecule nature, all chemical shifts of BMLEP showed sharp peaks with distinctive splitting patterns, attributed to the rotational mobility of its functional groups. It is reasonable to assume that these chemical shifts will remain the same in the polymer, albeit in less sharp and distinctive forms. Corresponding chemical shifts on the ^{1}H-NMR spectrum for all functional groups in polilactofate were thus assigned as shown in Figure 5(a). The restricted motion of the functional groups in polymer chains yielded chemical shifts that were less resolved than those in BMLEP.

Although comparison with ^{1}H-NMR of BMLEP provided valuable insights into the chemical shifts of various functional groups linked to ethylphosphate, it was still difficult to conclusively assign individual peaks within a cluster of overlapping peaks, such as peaks numbered 3, 6, and 8, and peaks 7, 9, and 11 in Figure 5(a). For this purpose the ^{1}H–^{1}H COSY NMR method was used to correlate chemically linked groups and help assign appropriate peaks on polymer NMR spectra. For example, correlation E in Figure 5(b) was used to identify the lactide groups linked to phosphoester linkages in the copolymers and assign peaks numbered 7 and 8 in Figure 5(a).

Upon completion of all chemical shift assignments, the integral values of methyl H peaks at 1.20, 1.36, and 1.58 ppm were used to determine the ratio among PG, ethylphosphate, and lactide moieties in the polyphosphoesters, respectively. As shown in Table I, polymer compositions calculated from NMR integral data matched very well with the composition of the starting materials. The number of lactide units in the polymer chain was further estimated by dividing the integral of lactide methine H peak in the main chain (5.1

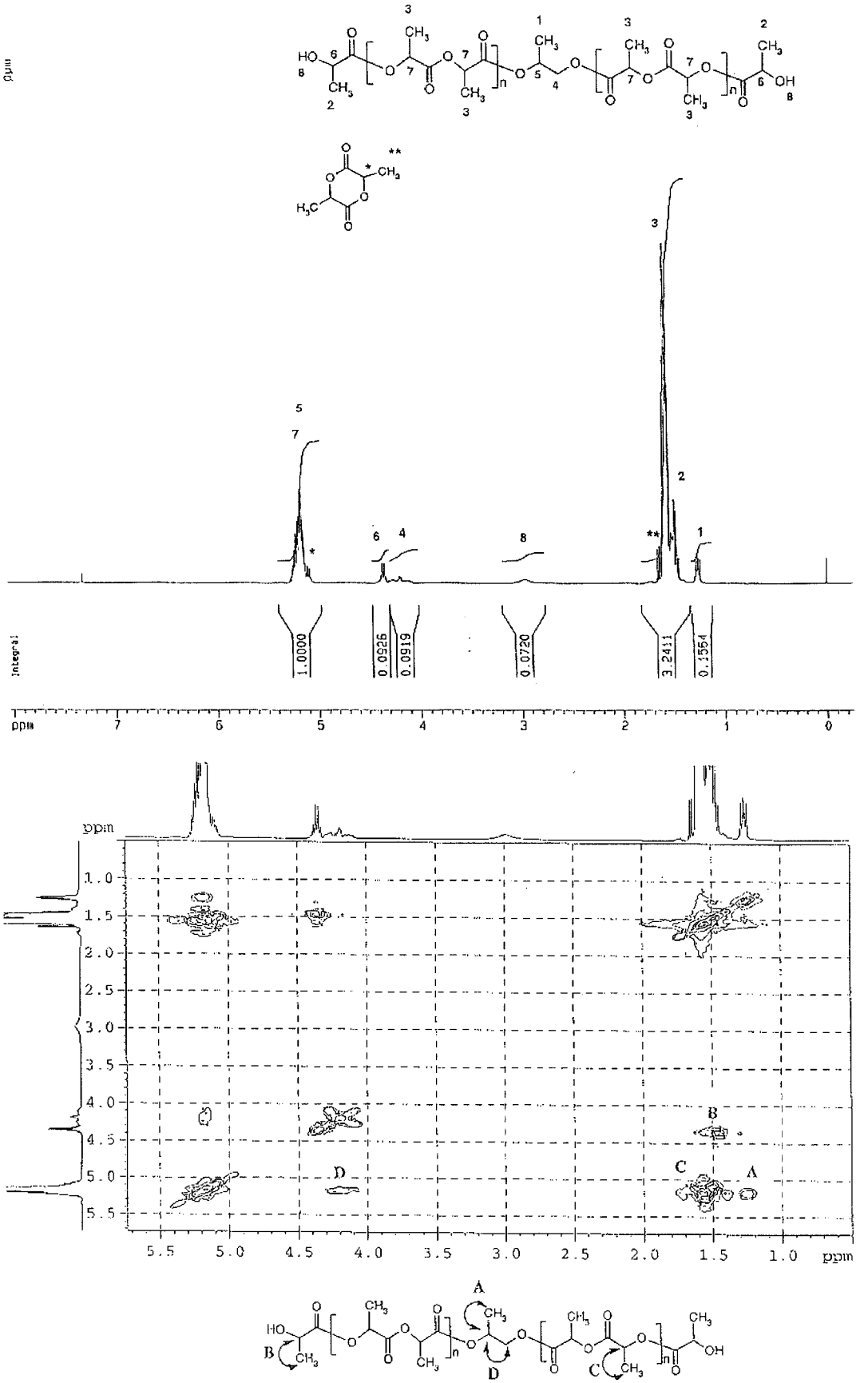

Figure 3 (a) ^{1}H-NMR with peak assignment and (b) ^{1}H–^{1}H COSY NMR with correlations for propylene glycol initiated lactide prepolymer.

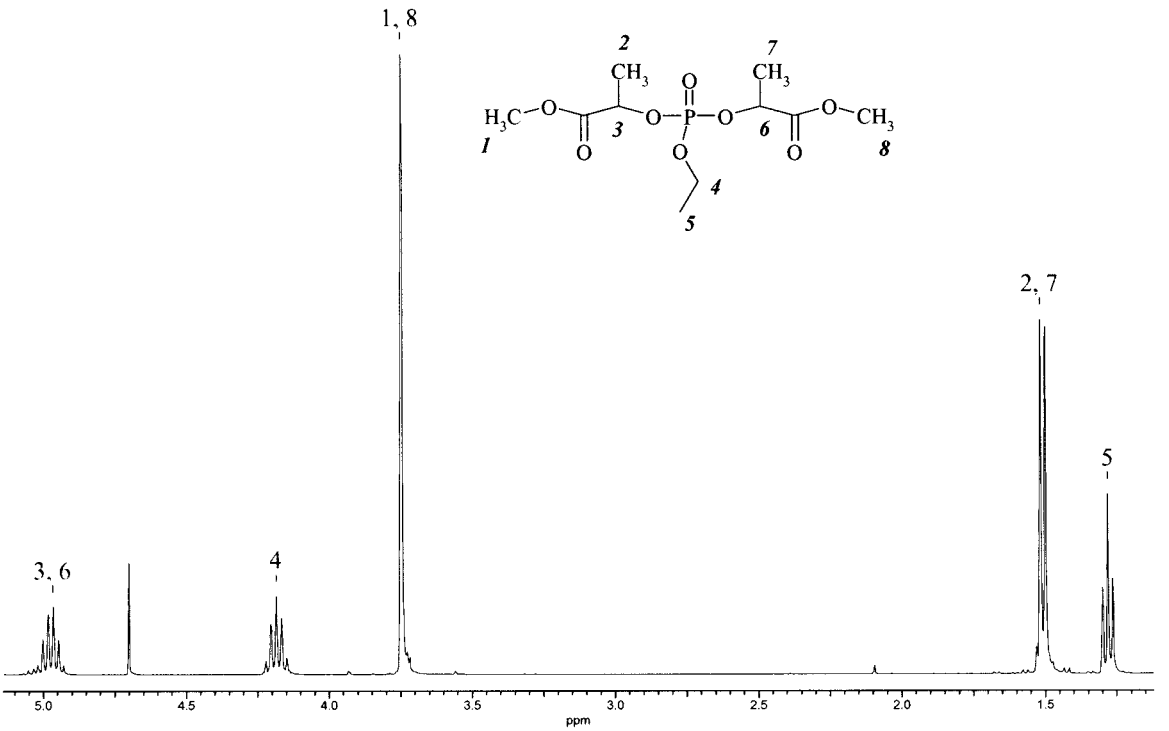

Figure 4 ^{1}H-NMR and peak assignments for BMLEP.

ppm) by that located at the end of the chain (4.5 ppm). This number was used to calculate the number-average molecular weight (M_n) of the polymers. As shown in Table I, excellent correlation exists between M_n estimated from the NMR data and that predicted from the feed ratio of the starting materials. Such a correlation is valid only when the polymerization proceeds to near completion. As confirmed by NMR of the prepolymers, PG and approximately 98% lactide were converted to the prepolymer form; thus the charge ratio of the monomers can be used to estimate M_n of the prepolymers. It was also observed that M_n of the prepolymers calculated from NMR data was consistently lower than that obtained from GPC. This discrepancy is likely caused by the fact that M_n measured by GPC is calculated relative to the polystyrene standards, which have a different hydrodynamic radius and configuration compared to polyphosphoester copolymers.

^{1}H-NMR assignment of polilactofate made using bulk polycondensation

Figure 6 shows a typical ^{1}H-NMR of polilactofate made using a bulk polycondensation process. Comparisons of its NMR spectrum with that of a polymer prepared by solution polymerization [Fig. 5(a)] and that of BMLEP (Fig. 4) revealed several additional peaks and different integration ratios between the known peaks. These new peaks were attributed to the side reactions occurring in a bulk polymerization process. The ratio of methyl H peaks of ethoxy of the phosphoester and PG decreased, suggesting removal of the ethoxy side group from the phosphoesters after the side reaction. The major difference between the bulk polycondensation and solution polymerization processes is the use of base and catalysts (TEA/DMAP) to capture hydrogen chloride (HCl) released during the reaction. In the bulk polycondensation, HCl gas generated was supposedly removed by agitation and nitrogen purge. However, relatively high viscosity of the polymer melt could impede the gas diffusion from the reaction mixture. The combination of a strong acidic HCl gas and a high reaction temperature led us to propose the reaction mechanism shown in Figure 7. First, protonation of the phosphoester by HCl makes it more prone to a nucleophilic attack. At a high temperature, the chlorine anion (Cl^-) could serve as a nucleophile to attack the methylene site of the ethoxy group on the phosphoester linkage (*a* in Fig. 7), giving rise to a P—OH structure and releasing chloroethane. This mechanism could explain the decrease of the methyl H peak of ethylphosphate on the ^{1}H-NMR as shown in Figure 6. Similar side reactions (*b* in Fig. 7) may also be expected at other sites of polilactofate during the bulk polycondensation, but to a lesser extent because of more steric hindrance.

To confirm the above proposed reaction mechanism, HCl gas was passed through BMLEP and the product profile was analyzed using ^{1}H-NMR. BMLEP

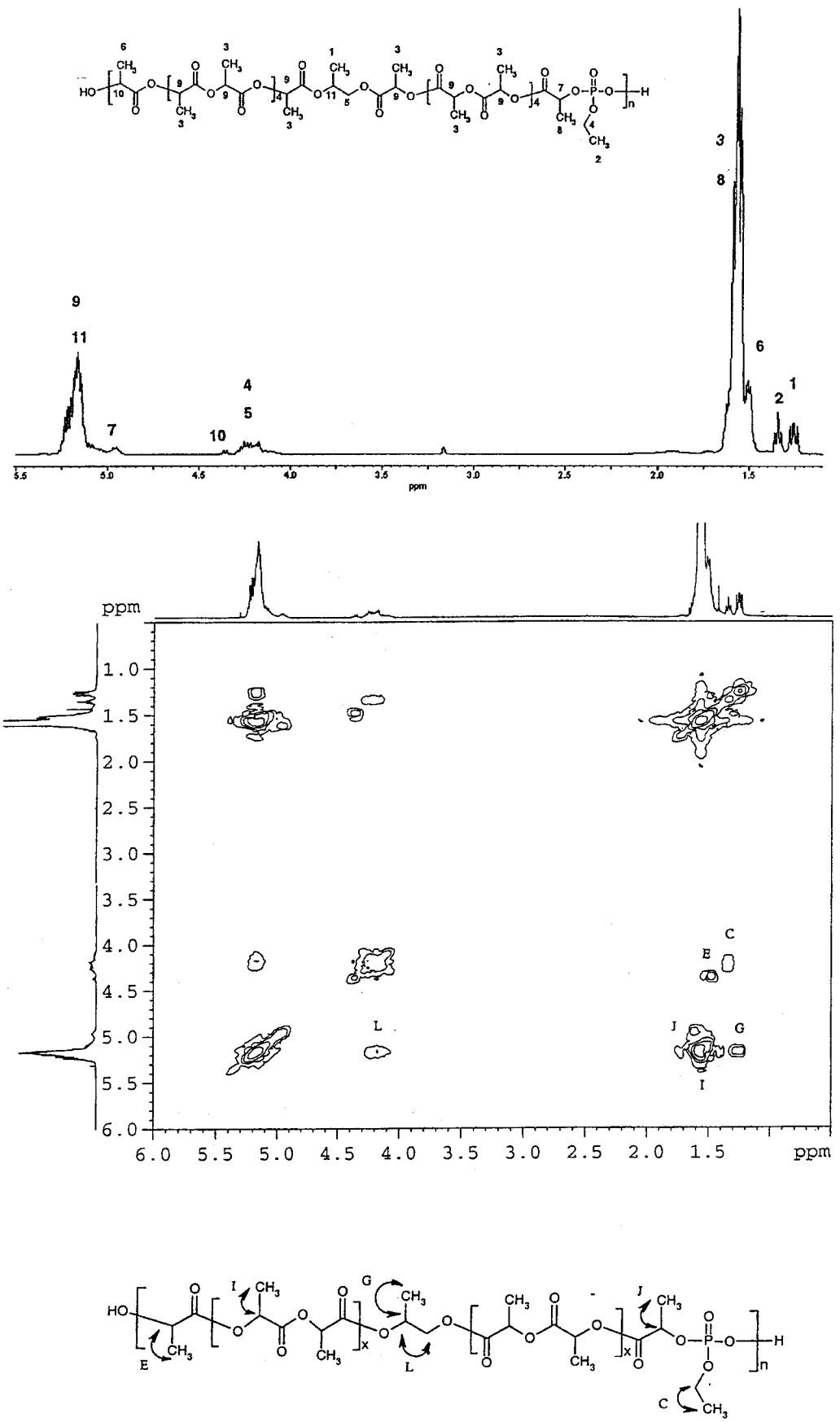

Figure 5 (a) ^{1}H-NMR with peak assignment and (b) ^{1}H–^{1}H COSY NMR with correlations for polilactofate made using solution polymerization process.

TABLE I
Molecular Weights of Both Prepolymer and Polymer Determined from Different Methods

Polymer	LA : PG : EDP feed ratio	LA : PG : EDP estimated from NMR	M_w GPC	M_n GPC	M_n NMR	M_n Predicted
Prepolymer-1	2.5 : 1 : 0	2.3 : 1 : 0	1018	776	419	436
Prepolymer-2	5 : 1 : 0	4.8 : 1 : 0	1582	1328	757	796
Prepolymer-3	10 : 1 : 0	9.8 : 1 : 0	3212	2518	1438	1516
Polymer-1	10 : 1 : 1	9.9 : 1 : 0.92	25100	13400	8500	N/A
Polymer-2	10 : 1 : 1	9.8 : 1 : 0.93	31700	9500	9500	N/A

indeed underwent rapid acidolysis in a manner similar to that depicted in Figure 7. The new peaks observed in the acidolysis of BMLEP matched those seen on ^{1}H-NMR of polymers synthesized by bulk polycondensation. This confirms the harmful effects of HCl gas on the purity of the polyphosphoester copolymers. The use of an acid acceptor (TEA) in solution polymerization, combined with the low temperature, eliminated the occurrence of such side reactions. NMR simulation studies were also performed using ACD software to predict ^{1}H-NMR spectra for some of the structures that may result from these side reactions. The simulations predicted chemical shifts of the lactate groups linked to P—OH linkages at about 3–4 ppm range on ^{1}H-NMR spectra. This agreed with the additional peaks seen for the polymers made by a bulk polycondensation process.

^{31}P-NMR assignment for polilactofate

The ^{31}P-NMR spectrum of the polilactofate made from the solution polymerization using racemic DL-lactide

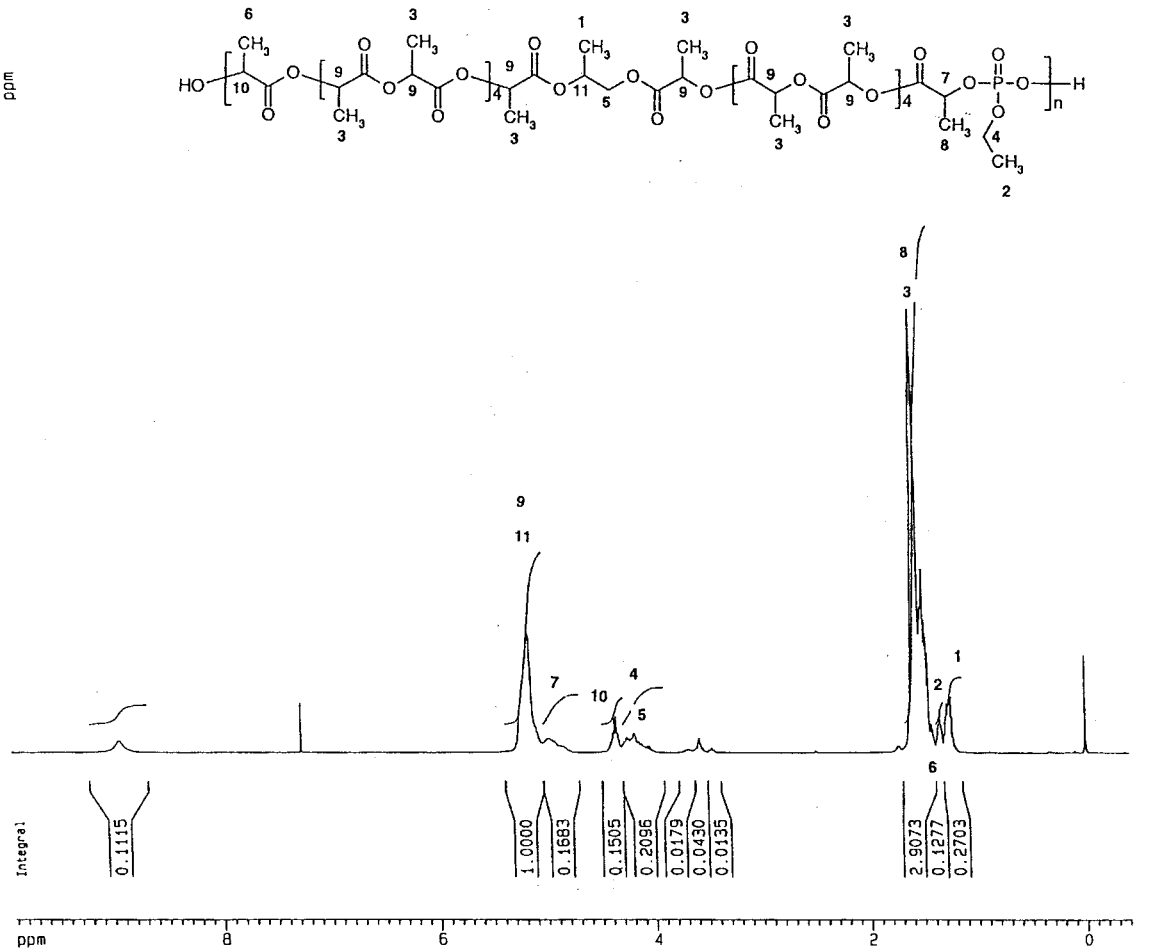

Figure 6 ^{1}H-NMR of polilactofate made using bulk polycondensation process.

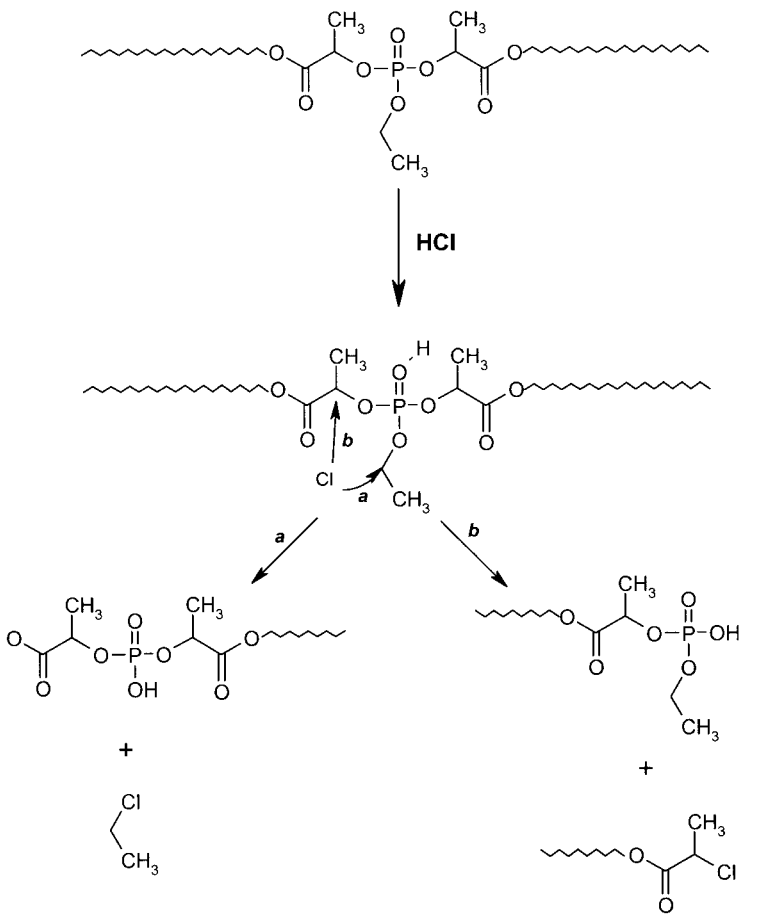

Figure 7 Proposed mechanism of HCl induced cleaving reactions at the phosphoester linkage in the polymer chain during bulk polycondensation.

as the monomer showed a set of three peaks: −1.6, −1.9, and −2.4 ppm [Fig. 8(a)]. To understand the origin of the three peaks, a few BMLEP model compounds were synthesized. It is expected that because the phosphoester linkages in polilactofate are identical to those in BMLEP, similar if not identical ^{31}P-NMR spectra for both the polyphosphoesters and the monomeric model compounds should be observed. These model compounds were prepared according to the synthetic scheme in Figure 2 using *R*-methyl lactate, *S*-methyl lactate, and racemic methyl lactate, respectively. ^{31}P-NMR spectra [Fig. 8(b)] revealed that the two model compounds derived from both *R*- and *S*-methyl lactates had the same singlet chemical shift at −1.6 ppm, whereas that derived from racemic methyl lactate showed a set of three peaks at −1.6, −1.9, and −2.4 ppm, identical to those found for polilactofate. We speculate that such multiplicity is derived from a mixture of diastereoisomers generated in the synthesis when a racemic starting methyl lactate was used. In this case, four different diastereoisomers could be formed, that is, *R,R*-BMLEP or *R*-LA-P-*R*-LA (the same as that made from *R*-methyl lactate), *S,S*-BMLEP or *S*-LA-P-*S*-LA (the same as that made from *S*-methyl lactate), *R,S*-BMLEP or *R*-LA-P-*S*-LA, and *S,R*-BMLEP or *S*-LA-P-*R*-LA (Fig. 9). The 1.6-ppm peak can be assigned to *R*-LA-P-*R*-LA and *S*-LA-P-*S*-LA, whereas the −1.9 and −2.4 ppm peaks are likely the result of the other two diastereoisomers, *R*-LA-P-*S*-LA and *S*-LA-P-*R*-LA. With respect to the phosphorus atoms, those in *R*-LA-P-*R*-LA and *S*-LA-P-*S*-LA are not chiral, whereas those in *R*-LA-P-*S*-LA and *S*-LA-P-*R*-LA are chiral. Therefore, *R*-LA-P-*R*-LA and *S*-LA-P-*S*-LA are identical with regard to the chirality around the phosphorus atom. On the contrary, *R*-LA-P-*S*-LA and *S*-LA-P-*R*-LA are in fact two different enantiomers relative to the phosphorus atoms. These might explain why *R*-LA-P-*R*-LA and *S*-LA-P-*S*-LA have the same chemical shift (both at −1.6 ppm) and *R*-LA-P-*S*-LA and *S*-LA-P-*R*-LA have different chemical shifts (−1.9 and −2.4 ppm) in ^{31}P-NMR spectra. Such a peak-splitting pattern caused by stereoelectronic variations on phosphoester moiety have been observed for other biomacromolecules such as DNA.[18] The three peaks observed for the diastereoisomer mixture correlated well with the peaks observed for poli-

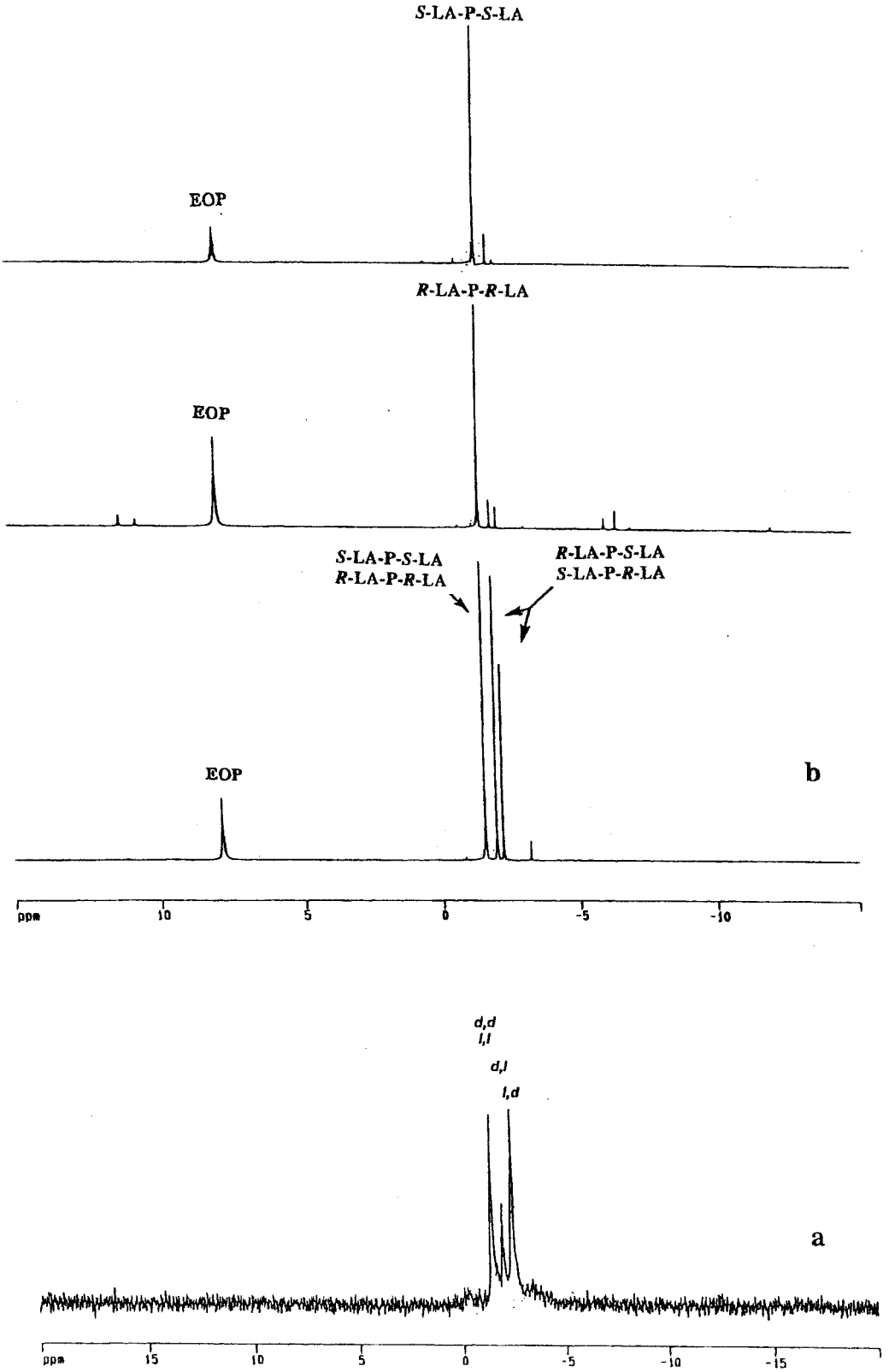

Figure 8 ^{31}P-NMR spectra of (a) DL-polilactofate and (b) BMLEP model compounds.

lactofate [Fig. 8(a)]. Furthermore, when polilactofate was synthesized using just L-lactide (instead of DL-lactide), the resulting polymer has a single peak that coincided with the single peak of the *S*-LA-P-*S*-LA peak. Based on these observations, the three peaks observed for DL-polilactofate were attributed to the

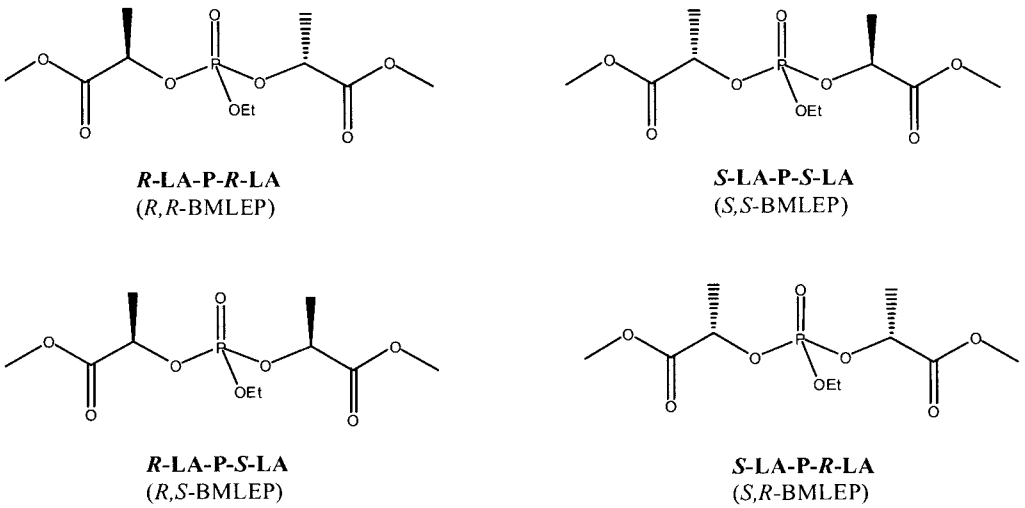

Figure 9 Four possible isomers when making model compounds from racemic methyl lactate.

combination of DD- or LL- (both of which could have the same peak shift), DL-, and LD-lactides linked to ethylphosphate.

CONCLUSIONS

This study presents a comprehensive approach to quantifying the structure and composition of complex biomedical-grade copolymers synthesized using multiple monomers. In particular, two-dimensional ^1H–^1H COSY NMR analysis of the polyphosphoester copolymers elucidated the identities of the overlapping chemical shifts on regular ^1H-NMR spectra. The results revealed the occurrence of side reactions when the polymer is produced using a bulk polycondensation process. In contrast, solution polymerization of the polyphosphoester copolymers, when carried out at low temperatures and in the presence of acid acceptors, is free of such side reactions and yields polymers with high purity and quantifiable compositions. Number-average molecular weight (M_n) of the polymers can be accurately estimated by the ^1H-NMR method when the polymerization proceeds to near completion. M_n of polyphosphoester copolymers estimated by the NMR method is consistently lower than that measured by the GPC method using monodisperse polystyrene as a calibration standard. Use of model compounds with identical phosphoester linkages to the copolymers is crucial in elucidating the three-peak patterns on ^{31}P-NMR spectra of polilactofates synthesized from racemic DL-lactide. These studies strongly suggest that ^{31}P-NMR chemical shift pattern of polilactofates results from stereochemical effects caused by the asymmetry of DL-lactides linked to ethylphosphate. The comprehensive NMR methods used in the study, particularly the model compound approach, may be extended to the composition analysis of other complex phosphorus-containing polymers such as polyphosphonates and polyphosphites.

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