Bulgarian Chemical Communications, Volume 52, Issue 1 (pp. 129-137) 2020 DOI: 10.34049/bcc.52.1.5197

Synthesis of poly-(alkyleneterephthalate-co-alkylenephosphate)s and their blends with a linear polyurethane

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Received July 25, 2019; Revised August 13, 2019

Polyphosphoesters present a family of synthetic biodegradable polymers that are recognized as attractive candidates for biomaterials development. Novel poly(alkyleneterephthalate-co-alkylenephosphate)s were prepared from 1,4-bis(2-hydroxyethyl)terephthalate, poly(tetrahydrofuran) (average Mn~650) as diol co-monomers in a polycondensation process with ethyl dichlorophosphate and terephthaloyl chloride. ^{1}H, $^{31}P\{H\}$ and ^{31}P NMR spectral data were used for elucidation of the copolymer structure and composition. Products with varying ratios of the phosphate units to the phthalate segments from 1.5 to 4 and number average molar masses in the range of 4500 g/mol to 6800 g/mol were synthesized. Their film-forming properties were enhanced *via* blending with linear polyurethane. The blended materials displayed Tg values and relative hydrophobicity dependent on the content of the phosphate segments. The established trends in structure-properties relationship could be used for design of biomaterials with targeted applications.

Keywords: polyphosphoesters, copolymers, polymer blends, NMR, DMA

INTRODUCTION

The development of novel biomedical technologies such as tissue engineering, drug delivery, regenerative medicine, nanomedicine, etc. requires versatile biodegradable materials as a platform to build on. The complexity and the broad range of applications pose the need for fabrication of new polymers with tailored structure and functionalities. Some of the inherent properties of polymeric biomaterials that can affect their performance include material composition, molecular weight, solubility, hydrophilicity/ hydrophobicity, water absorption, degradation, etc. Since 1960s when the first synthetic poly(glycolic acid) based sutures were implemented, extensive research on design of biodegradable polymer materials based on polyesters, polyurethanes, polyanhydrides, poly(alkyl cyanoacrylate)s, polymer blends or composites has been carried out [1].

Polyphosphoesters (PPEs) present a family of synthetic biodegradable polymers with a variety of attractive properties [2]. The common structural characteristics of the PPEs are the phosphoester bonds that link the building units of the polymer backbone. Therefore, they have been recognized as attractive candidates for biomaterials manufactured as polymers susceptible to both hydrolytic and enzymatic degradation under physiological conditions [3]. The physico-chemical properties of these polymers can be adjusted by varying either the backbone building units or side chains structure [4-6]. PPE polymers have been successfully used for controlled drug and gene delivery [7-10].

The synthetic flexibility of polyphosphoesters allows for the development of copolymers with structural versatility. The polycondensation is a widely studied method to synthesize polyphosphoesters. The reaction proceeds between diols and diesters of H-phosphonic acid, phosphoric dihalides, or phosphoric acid. The biodegradable polilactofate was obtained by bulk or solution polycondensation of dihydroxy(oligolactide) with ethyl dichlorophosphate and the product composition was thoroughly analyzed [11]. The glass transition temperature of the copolymers was found to be inversely proportional to the weight percentage of the phosphoester segment. The co-polymers were also found to be more hydrophilic due to the presence of ethylphosphate groups in the backbone.

PPEs derived from bis(2-hydroxyethyl) terephthalate (BHET) and ethyl dichlorophosphate (ECP) with addition of terephthaloyl chloride (TC) as a chain extender were obtained and studied in the preparation of microspheres or conduits [12, 13]. Biocompatibility studies indicated that these PPEs (P(BHET/ECP/TC)) were non-toxic but the implanted devices underwent fragmentation and partial rupture.

Linear polyurethanes (PUs) are an important class of thermoplastic elastomers, which consist of an alternating flexible component (macrodiol) called soft segment, and a stiff component derived from diisocyanate and a chain extender, called hard segment. The nature of hydrogen bonding in the hard segment causes a strong mutual attraction leading to formation of hard and soft segment

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domains. Hard domains act as thermoreversible physical crosslinks and provide for the thermoplastic and elastomeric characteristics of the PU. Therefore, their molecular structure affords a combination of mechanical flexibility and chemical stability that captured the attention of researchers in the field of biomaterials [14, 15].

The aim of the present investigation is the synthesis of poly(alkyleneterephthalate-co-alkylenephosphate)s as new members of the PPE family. The results on their preparation and structural characterization applying NMR technique are reported. To improve PPE film-forming properties and manipulate their physico-chemical characteristics blends with linear polyurethane were prepared and tested.

EXPERIMENTAL

Materials and Methods

Terephthaloyl chloride (TC), 1,4-bis(2-hydroxyethyl) terephthalate (BHET), poly(tetrahydrofuran) (PTHF, average Mn~650), 4-dimethylaminopyridine (DMAP), ethyl dichlorophosphate (ECP), chloroform, tetrachloroethane were purchased from Sigma-Aldrich. Linear polyurethane (PU) with terminal hydroxyl groups and dynamic viscosity 1800 mPa.s (15 % solution in butan-2-one at 23 °C) was kindly supplied by Specialty Polymers Ltd. (Bulgaria). PTHF, BHET and tetrachloroethane were dried prior to use.

Synthetic procedures

Synthesis of poly(alkyleneterephthalate-co-alkylenephosphate)s. The poly(alkyleneterephthalate-co-alkylenephosphate)s were synthesized following a procedure reported by Mao *et al.* [16] with some modifications. The quantities of the starting monomers in the reaction feed mixture are listed in Table 1. DMAP was used as catalyst in equivalents to the sum of the diols moles. The general procedure used is as follows. Under an argon stream, a two-neck round-bottom flask fitted with a condenser and a dropping funnel was charged with a solution of BHET, PTHF and DMAP in 10 mL tetrachloroethane. The mixture in the flask was cooled down to – 15 °C. A solution of ECP in 5 mL of tetrachloroethane was added dropwise to the flask through the funnel. Following the addition of the ECP, the mixture was stirred first at room temperature for 3 h and then at 45 °C for 6 h. Then the mixture was cooled to room temperature and a solution of TC in 5 mL of tetrachloroethane was added to the flask. The temperature was gradually brought up to 50 °C and allowed to react for 12 h, followed by heating at 65°C for additional 2 h. The mixture was cooled down to room temperature, washed three times with saturated NaCl solution and once with distilled water. The organic layer was concentrated and quenched with ether. The precipitate was dried under vacuum at 40°C overnight to give a copolymer as a white solid. The yield of poly(alkyleneterephthalate-co-alkylenephosphate)s varied between 60% and 65%. The obtained products were assigned as PTPm/n, where m/n was the molar ratio of TC to ECP.

Table 1. Content of the starting monomers in the reaction feed mixture.

Product code	Monomers' content in the reaction feed mixture			
	BHET	PTHF	ECP	TC
PTP4/6	1.5 g 5.89×10^{-3} moles	0.4261 g 0.66×10^{-3} moles	0.6399 g 3.93×10^{-3} moles	0.5316 g 2.62×10^{-3} moles
PTP3/7	1.5 g 5.89×10^{-3} moles	0.4261 g 0.66×10^{-3} moles	0.7467 g 4.58×10^{-3} moles	0.399 g 1.96×10^{-3} moles
PTP2/8	1.5 g 5.89×10^{-3} moles	0.4261 g 0.66×10^{-3} moles	0.907 g 5.75×10^{-3} moles	0.266 g 1.31×10^{-3} moles

Preparation of films from poly(alkyleneterephthalate-co-alkylenephosphate)s-polyurethane blends. Solutions of poly(alkyleneterephthalate-co-alkylenephosphate)s (PTPn/m) and PU in chloroform (0.50 g in 3 ml) were mixed and stirred for 15 min. Then the mixed solutions were casted in PTFE molds and air dried. The films were additionally dried under reduced pressure overnight. A PU film was prepared by casting of PU solution (1.0 g in 6 ml chloroform) and dried under the same conditions.

For contact angle measurements thin polymer films were obtained on glass slides by spin-coating of 7 % solutions in chloroform.

Characterization techniques

NMR spectroscopy. ^{1}H, ^{31}P and $^{31}P\{H\}$ NMR spectra of the synthesized copolymers were recorded on a Bruker Avance II+600 MHz instrument in tetrachloroethane-d_2 at a temperature of 293 K.

Contact angle measurements. The water contact angle of the polymeric films was determined using an Easy Drop DSA20E Krüss GmbH apparatus (Germany). A drop of deionized water (10 μL) was deposited on the surface of the films. Images for temporal evolution of the contact angle value were taken. The average value of the contact angle was determined based on 20 different measurements for each sample.

Dynamic mechanical analysis. The measurements were performed on DMA Q 800 instrument (TA Instruments) in iso-force mode. Specimens with approximate dimensions of 17 × 7 × 0.26 mm were cut off from the prepared films of the PTPm/n-PU blends and PU. Force of 0.5 N was applied to the specimens that were cooled down to -80 °C and held for 3 min. Then displacement (in μm) and relaxation modulus were measured as a function of temperature which increased at a rate of 3 °C/min until displacement reached 2000 μm.

RESULTS AND DISCUSSION

Synthesis and NMR characterization of poly(alkyleneterephthalate-co-alkylenephosphate)s

The polycondensation process of the two diols (BHET and PTHF) and the two acid chlorides (ECP and TC) was performed as a two-step process. At the first step the diols were condensed with ECP and the obtained oligomers were reacted with TC. This reaction scheme reduces the probability for long polyterephthalate blocks to be obtained in the copolymer backbone due to higher reactivity of TC compared to ECP. It was reported by Mao *et al.* [16] that the addition of both chlorides at the same time to the reaction feed resulted in a copolymer displaying a high melting point (above 180 °C) and decreased solubility, especially for ratios TC:ECP≥0.25. The reaction scheme is presented in Fig. 1 and the mole ratio of the reactants is given in Table 2. The diols in mole ratio BHET:PTHF = 9 (mass ratio BHET:PTHF = 3.5) and DMAP in equivalents to the sum of the diols moles were dissolved in tetrachloroethane. Preliminary experiments proved tetrachloroethane to be a better solvent for the resulting copolymer than dichloromethane or chloroform. The solution was cooled to -15 °C and ECP was added drop-wise. The reaction proceeded at room temperature for 3 h and at 45 °C for 6 h. When ECP was exhausted (detected by NMR) the second chloride was added followed by stirring at elevated temperatures up to 65 °C for a total of 14 h. The entire synthetic experiment was performed under dry argon atmosphere. The isolated and purified product was structurally characterized applying ^{1}H, ^{31}P and $^{31}P\{H\}$ NMR technique.

Three copolymers were synthesized applying different ratios between TC and ECP. It was proved by the NMR data that the composition of the obtained copolymers was close to the ratio of the starting monomers in the reaction mixture (Table 2).

Table 2. Composition of the reaction feed mixture and of the obtained copolymer.

Product code	Reaction feed mixture		Copolymer composition*		M_n*, g/mol
	Mole ratio BHET:PTHF	Mole ratio TC: ECP	Phthalate units: phosphate units	Phthalate units: PTHF units	
PTP4/6	9:1	4:6	1:1.5	12.9:1	4500
PTP3/7	9:1	3:7	1:2.3	11.8:1	5600
PTP2/8	9:1	2:8	1:3.9	10.5:1	6800

*Values were calculated on the basis of the ^{1}H NMR data for the copolymer products.

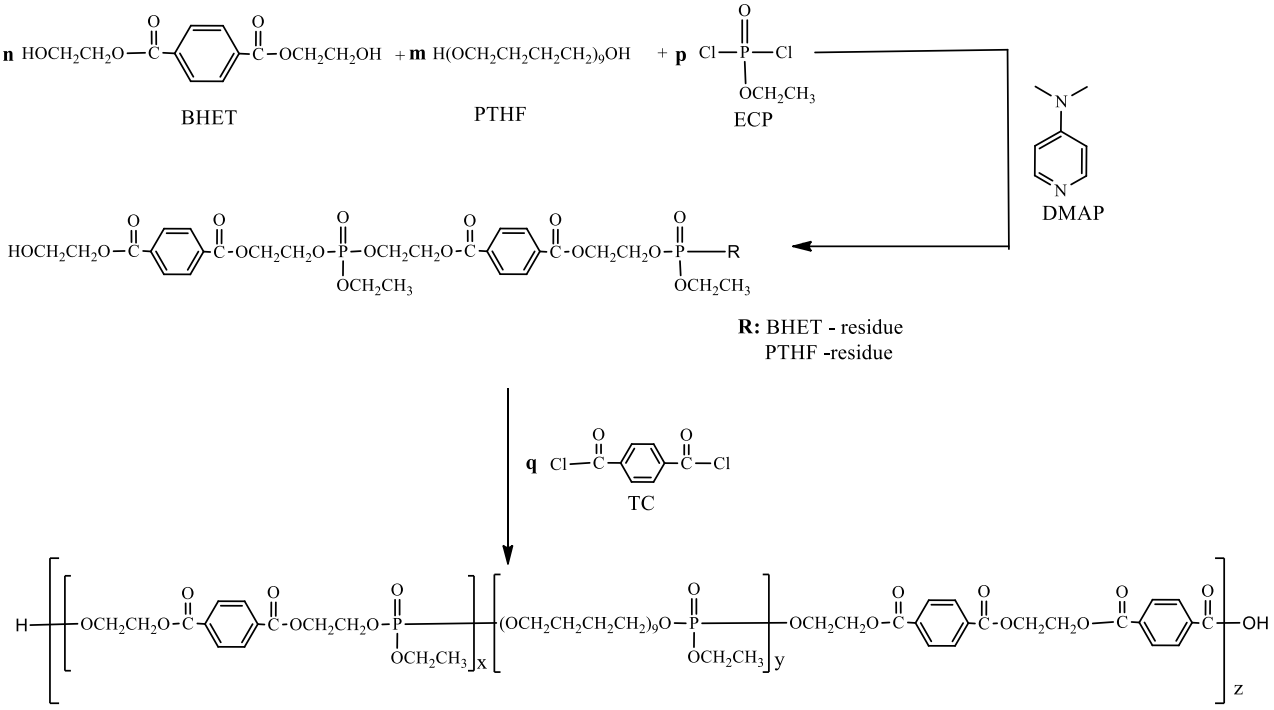
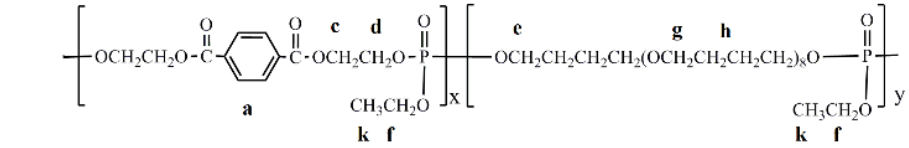


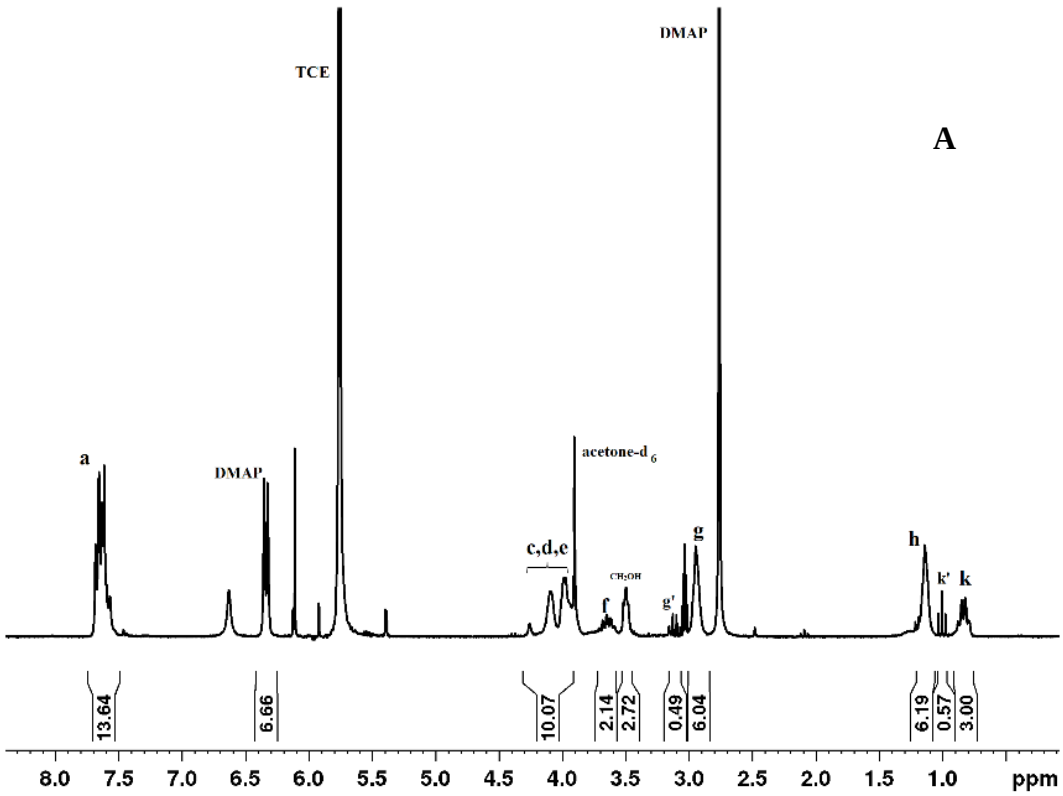
Fig. 1. Two-step synthetic scheme for the preparation of poly(alkyleneterephthalate-co-alkylenephosphate)s.

At the first step of the polycondensation process, i.e. when the reaction proceeded between ECP and the two diols and the latter being in excess, oligomeric products were obtained. The ^{1}H and ^{31}P{H} NMR spectra of the reaction mixture with mole ratio ECP:TC=8:2 after 9 h reaction time are presented in Fig. 2 (A and B). The spectral data were used to register the degree of ECP conversion, as well as to determine the structure and the number average molar mass of the obtained oligomers. The assignment of the signals is presented in Fig. 2. The ^{31}P{H} NMR spectrum (Fig.2B) evidences two types of P-atoms, which can be assigned to triester phosphate structures in the region from 0.16 ppm to -0.70 ppm and diester chlorophosphate at -5.06 ppm. This assumption is supported by the presence of two couples of signals for the pendant ethyl group to the P-atom in the ^{1}H NMR spectrum (Fig. 2A): (i) a quartet at 3.11 ppm and a triplet at 1.00 ppm for the hydrogens in the CH_2 and CH_3 groups, respectively, in the end diester phosphate and (ii) the corresponding multiplets in the region 3.79-3.58 ppm and 0.90-0.75 ppm (overlapped triplets) for the triester phosphates. The triester phosphates present 84 mol% that means, 84% of the starting ECP has undergone two substitution reactions forming two new ester bonds, while the rest 16% of the P-centers were terminal reactive moieties. The signal at 3.50 ppm is assigned to the methylene protons adjacent to the hydroxyl group in BHET unit ($HOCH_2$-) and can be used for calculation of the molecular mass of the oligomers obtained at the first stage. The latter is determined taking into consideration the sum of integral intensities of the signals for the ester methylene protons in the region from 4.30 ppm to 3.92 ppm and the integral intensity of the signal at 3.50 ppm used to calculate the integral intensities for one H-atom from the ester or the end C$\underline{H_2}$OH groups, respectively. From their ratio it was calculated that the number average molar mass of the oligomeric species was about 900 g/mol.

In the second step the process continued with the addition of the second chloride and polycondensation of the oligomers with TC for obtaining a polymer product. Fig. 3A presents the ^{1}H NMR spectrum of the product PTP2/8. The signal at 8.00 ppm is due to the H-atoms of the aromatic rings while those at 3.36 ppm and 1.50 ppm are due to methylene protons in the PTHF segments. The ratio of the integral intensity assigned to one hydrogen from the aromatic structures to that from the tetramethylene oxide units is about 11 which is close to the mole ratio of (BHET+TC)/PTHF in the feeding mixture. The integral intensity of the signal at 4.60 ppm assigned to the H-atoms from the ester ethylene residues between two aromatic rings and that of the signals from 4.45 ppm to 4.00 ppm referred to the carboxy- and phosphoester methylene hydrogens were used for calculation of the content of the terephthalate and phosphate units. The calculated ratio from the spectral data is 3.9 which is consistent with the content in the starting mixture. The signal of the end C$\underline{H_2}$OH groups appears at 3.72 ppm. It was used for the determination of the number average

molar mass of PTP2/8 copolymer as in the case of the oligomeric product at the first stage. The average number of the building segments of the polymer backbone is about 17. Taking into consideration the polymer composition its number average molar mass was calculated equal to 6 800 g/mol.





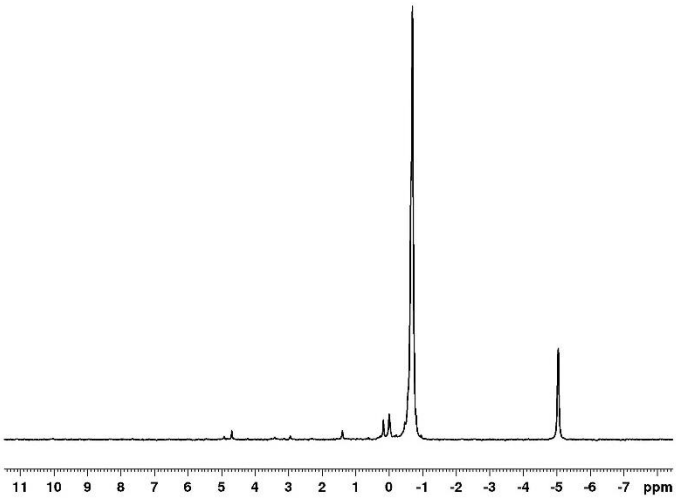


Fig. 2. ^{1}H (A) and $^{31}P\{H\}$ NMR (B) spectra of the reaction mixture with mole ratio ECP:TC=8:2 after 9 h reaction time

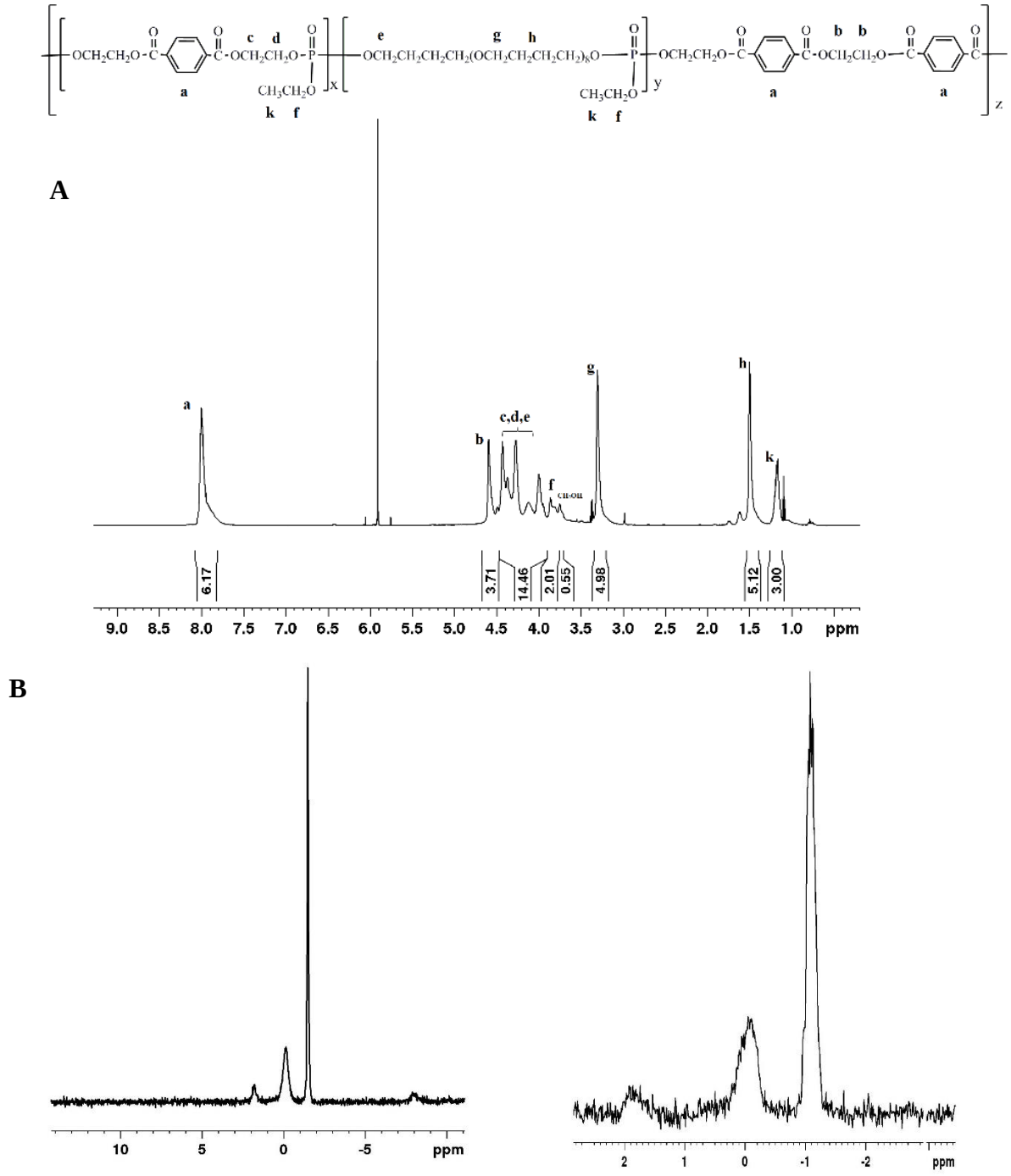


Fig. 3. ^{1}H (A), ^{31}P{H} (B) and ^{31}P{H} NMR (C) spectra of the copolymer PTP2/8.

The ^{31}P{H} NMR spectrum (Fig. 3B) of the copolymer PTP2/8 shows signals in the region of the triester phosphate structures which is an expected result having in mind the reaction scheme of the process. It is seen in the ^{31}P NMR spectrum that the signal at -1.48 ppm is a septet (Fig. 3C) corresponding to a P-atom coupled to three methylene groups from the triester structure.

The other two copolymers displayed signals in both the ^{1}H and ^{31}P{H} NMR spectra in the same spectral regions as those for PTP2/8 discussed above. Fig. 4 presents the NMR spectra of the copolymer PTP4/6 obtained at the highest ratio of TC to ECP.

In a similar manner, the spectral data from the ^{1}H NMR spectrum were used for calculation of the ratios between the building structures in the copolymer backbone, as well as the number average molar mass of the product. The calculated values are listed in Table 2.

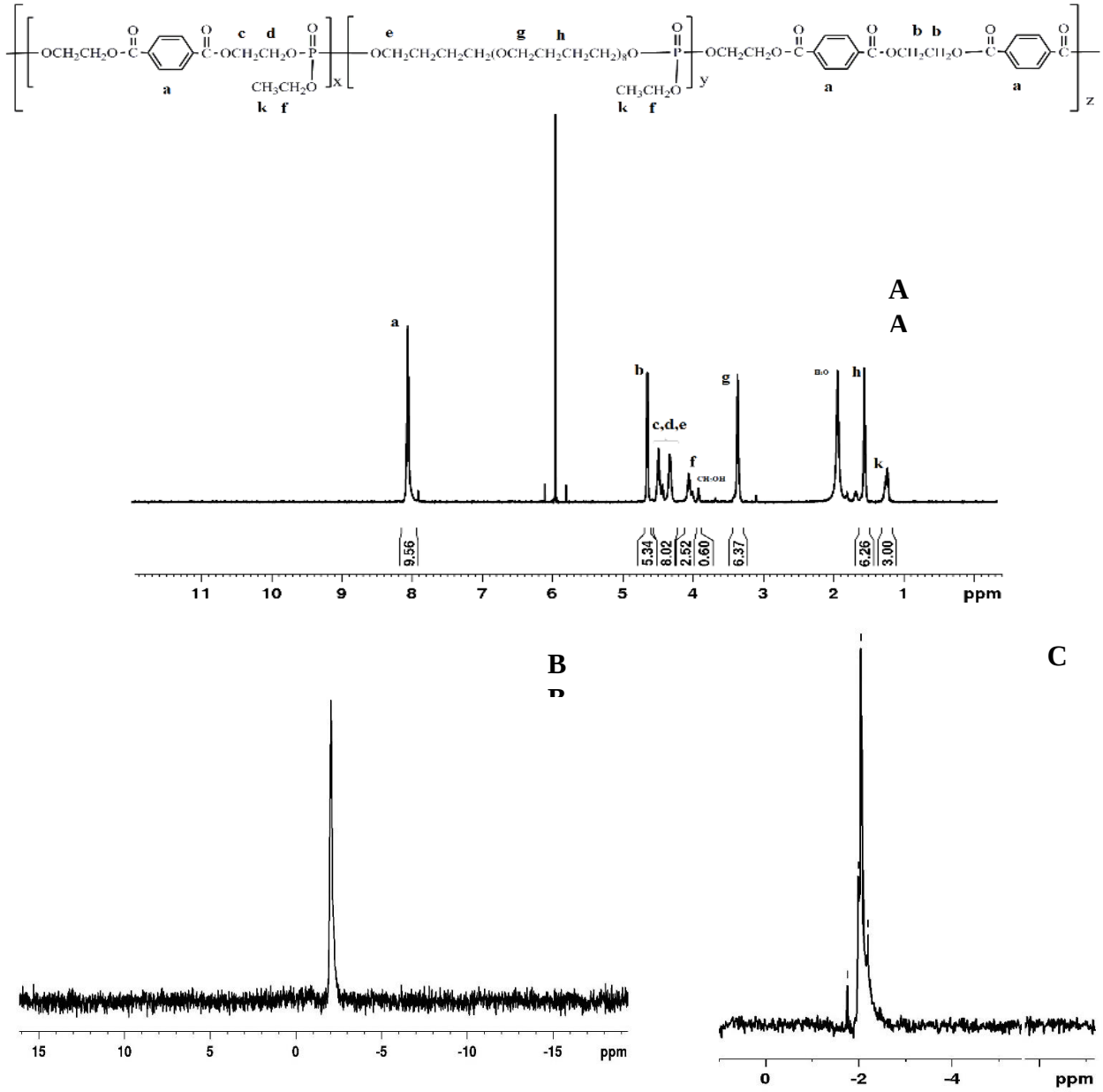


Fig. 4. ^{1}H (A), ^{31}P{H} (B) and ^{31}P NMR (C) spectra of the copolymer PTP4/6.

The ^{31}P{H} NMR spectrum (Fig. 4B) and the fine structure of the multiplet in the ^{31}P NMR spectrum (Fig. 4C) also evidenced the presence of the triester phosphate structures in the copolymer backbone.

Film preparation and characterization

Blending of polymers is a feasible route to impart new properties or enhance existing characteristics of the individual components of the blend. The attempts to prepare films *via* casting of PTP4/6 and PTP3/7 solutions failed while the film obtained from PTP2/8 displayed poor mechanical properties. Therefore, films were casted from the mixed solutions of PTPm/n and linear PU in chloroform. Rectangular samples, with approximate dimensions of 17 × 7 × 0.26 mm were cut off from the dried films and analyzed applying a DMA Q 800 instrument in iso-force mode. All samples were tested in a temperature sweep mode from –80 °C to 60 °C at a constant heating rate of 3 °C/min or until displacement reached 2000 μm.

During the DMA experiment, the instrument mechanically deforms the sample and the sample response to the deformation is monitored as a function of temperature. Fig. 5 presents the first derivative of the stress relaxation modulus as a function of temperature for the three blends. For comparison, the same experiment with neat PU was performed. The maximum of the curve denotes the

samples' Tg which for the neat PU is 7 °C. Blending of PU with PTP copolymers resulted into an increase in Tg but still its value was below 37 °C which means that the polymer blends retain their elastic behavior at temperatures below and close to the body temperature. The observed trend of the blends' Tg increase with the increase of the terephthalate fraction in the PTP could be assigned to the propensity of the terephthalate units to form ordered structures, as well as to the interactions between the PTP and PU macromolecules. It is known that the phosphoryl group is a strong proton acceptor and could form hydrogen bonds with the urethane segments. Similar trend was observed for the temperature of the necking on-set (Table 3). For two of the polymer blends, PTP3/7-PU and PTP4/6-PU, the necking phenomenon started at temperatures higher than the body temperature which is an indication that they would undergo elastic deformations at 37 °C at moderate stress. For PTP2/8-PU blend, the necking started at 32 °C, i.e. the material would exhibit plastic deformation at higher temperature. This performance could be a disadvantage for applying this blend composition in a device but could be advantageous if using the same composition in a drug delivery system to control the release rate of a bioactive component.

Table 3. Experimental data from the dynamic mechanical analysis of the blends.

Sample code	Tg (°C)	Temperature of on-set of necking (°C)
PU	7	42
PTP2/8-PU	10	32
PTP3/7-PU	12	40
PTP4/6-PU	25	48

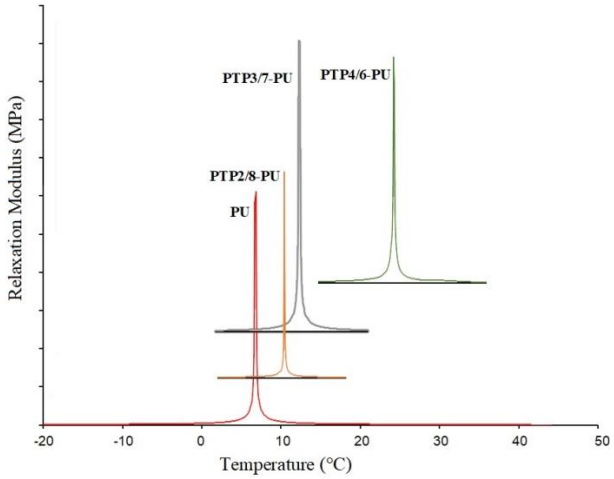


Fig. 5. Dependence of the stress relaxation modulus on temperature for the three blends and for a PU sample. Measurements were performed in iso-force mode (F= 0.5 N, heating rate of 3 °C/min).

Table 4. Data from the contact angle measurements for the PTP copolymers and PU, and their blends.

Sample code	Contact angle	Sample code	Contact angle
PU	69.4 ± 5.23	-	-
PTP4/6	52.8 ± 0.16	PTP4/6-PU	60.5±3.5
PTP3/7	34.7 ± 0.40	PTP3/7-PU	40.1 ± 4.31
PTP2/8	29.7 ± 0.24	PTP2/8-PU	31.8 ± 0.29

The relative hydrophobicity of the PTPm/n series and their blends was assessed by measuring the water-in-air contact angle. As it is seen from the determined contact angle values the hydrophilicity of the copolymers increased with the increase of the fraction of phosphate groups in the backbone. Similar trend was found for the polilactofate copolymers with main chain composed of oligolactide segments linked with ethylphosphate moieties [11]. The obtained blends of PTPm/n-PU

displayed contact angles with values between those measured for the PU and the corresponding PTP copolymer.

CONCLUSION

A series of new poly(alkyleneterephthalate-co-alkylenephosphate)s were prepared on varying the ratio of phosphate units to phthalate units from 1.5 to 4. The copolymer structure and composition were elucidated applying ^{1}H, $^{31}P\{H\}$ and ^{31}P NMR spectroscopy. The NMR data were used to calculate the number average molar masses of the obtained copolymers that were in the range of 4500 g/mol to 6800 g/mol. Blending with linear PU improved the film-forming properties of the copolymers. Dynamic mechanical analysis and contact angle measurements revealed that the Tg values and relative hydrophobicity of the materials depend on the content of the phosphate segments. It could be also concluded that *via* tuning the composition of the PTP/PU blends different biomedical applications of the newly developed materials could be attained.

Acknowledgement: *The authors gratefully acknowledge the support by the NSF of Bulgaria (Contract No DNTC/China 01/13/2016).*

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