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Synthesis and Characterization of Poly(Oxyethylene)S with (2-Benzoxazolon-3-yl)Acetyl End-Groups. Complex Formation with Polycarboxylic Acids

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SYNTHESIS AND CHARACTERIZATION OF POLY(OXYETHYLENE)S WITH (2-BENZOXAZOLON-3-YL)ACETYL END-GROUPS. COMPLEX FORMATION WITH POLYCARBOXYLIC ACIDS

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Key Words: (2-Benzoxazolon-3-yl)acetic Acid, Dicyclohexylcarbodiimide, 4-Dimetylaminopyridine, Poly(oxyethylene) with (2-benzoxazolon-3-yl-acetyl) End Group, Interpolymer Complexes

ABSTRACT

Chemical modification of poly(oxyethylene)s (MW from 600 Da to 3000 Da), leading to the obtaining of poly(oxyethylene)s with (2-benzoxazolon-3-yl)acetyl endgroups, is described. The corresponding diesters were synthesized in high yields-70-84% and degree of esterification-82-92% under mild conditions in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine as catalyst. The diesters were characterized by ^{1}H-NMR, ^{13}C-NMR and IR spectra, and SEC analysis. The relatively narrow molecular weight distribution was retained in the process of chemical modification. The complex formation between polyacrylic or polymeth-

acrylic acids and (2-benzoxazolon-3-yl)acetyl derivatives of poly-(oxyethylene)s was studied in dilute aqueous solutions by potentiometric titration and viscometry. The presence of (2-benzoxazolon-3-yl)acetyl end groups attached to the poly(oxyethylene)s chains results in a significant decrease of the critical poly(oxyethylene) chain length necessary for the formation of stable polymer-polymer complexes.

INTRODUCTION

Poly(ethyleneglycol) (PEG) is widely used as a carrier polymer because of its biocompatibility, solubility in water and in organic solvents, and its availability in a wide range of molecular weights [1, 2]. Drugs, plant growth regulators, and herbicides were covalently attached to PEG in order to prepare new macromolecular derivatives of these biologically active compounds combining the properties of both the polymer carrier and the low molecular weight compound. The complex formation between these derivatives and polyacids was studied as a possible route to creation of new materials for sustained release of bioactive agents [3-7].

Benzoxazolone and some of its derivatives are objects of numerous studies on the possibilities for their application as drugs and pesticides [8]. (2-Benzoxazolon-3-yl)acetic acid (BOAA) shows an analgesic activity [9, 10]. We found that the conjugates of BOAA with PEG (MW400) were very useful as substrates of the biocatalyst *Penicillin amidase* in the synthesis of cephem antibiotics [11, 12]. The conjugates were prepared by the dicyclohexylcarbodiimide (DCC) method without catalyst [11].

The present paper describes the synthesis of PEG esters of BOAA using poly(oxyethylene)s of molecular weight in the range 600-3000 ($POE_{600-3000}$) by the DCC method with 4-dimethylaminopyridine (DMAP) as a catalyst. The forma-tion of interpolymer complexes with polyacrylic (PAA) or polymethacrylic (PMA) acid is also reported.

EXPERIMENTAL

Materials

POEs of molecular weight of 600 Da and 1500 Da (Janssen) and 1000 Da, 2000 Da and 3000 Da (Fluka) were used. DMAP and DCC were Janssen products. BOAA was synthesized as previously described [13]. PAA and PMA were prepared by radical polymerization of the corresponding monomers in benzene at 60°C under N_2 with initiator α,α'-azoisobutyronitrile (AIBN). PAA molecular

weight was determined viscometrically in 2N NaOH at 25°C; $[\eta] = 1.05.10^{-3} M^{0.54}$ [14]. PMA molecular weight was determined viscometrically in 0.002 N HCl at 30°C; $[\eta] = 6.6 .10^{-4} M^{0.5}$ [15]. In the present study, the molecular weight of PAA and PMA were $5.3.10^5$ Da and $8.7.10^5$ Da, respectively. All other chemicals used were of laboratory grade.

Methods

Size-exclusion chromatography (SEC) analyses were performed on a Waters 244 apparatus equipped with a set of Ultrastyragel columns of pore sizes 100, 500, 1000 Å, in THF at 45°C, flow rate 1 ml/min, using double detection (differential refractometer and UV- λ_{max} 254 nm) and POE standards for calibration. $\overline{M}_n$ of the products obtained was determined by the method of vapor pressure osmometry (VPO) on a Knauer apparatus, Germany, in $CHCl_3$ at 45°C against benzil as standard.

^1H and ^{13}C-NMR spectra of polymers were recorded at 30°C on a Bruker spectrometer operating either at 250 MHz (^1H, in DMSO-d_6) or at 62.89 MHz (^{13}C, in $CDCl_3$). The chemical shifts are given in ppm from TMS using the following shift conversions: δ(DMSO-d_6) = 2.5 (TMS) and δ ($CDCl_3$) = 77.00 (TMS). The IR spectra were taken on a Perkin-Elmer 983G ratio recording spectrometer in $CHCl_3$. The UV spectra were recorded on UV-VIS Specord M40 spectrophotometer (Carl Zeiss, GmbH, Germany).

Differential scanning calorimetry (DSC) data were obtained with the Perkin-Elmer Delta Series DSC7 instrument. The samples were processed in the temperature range from -60° to 170°C at a scanning rate of 10.0°C/min.

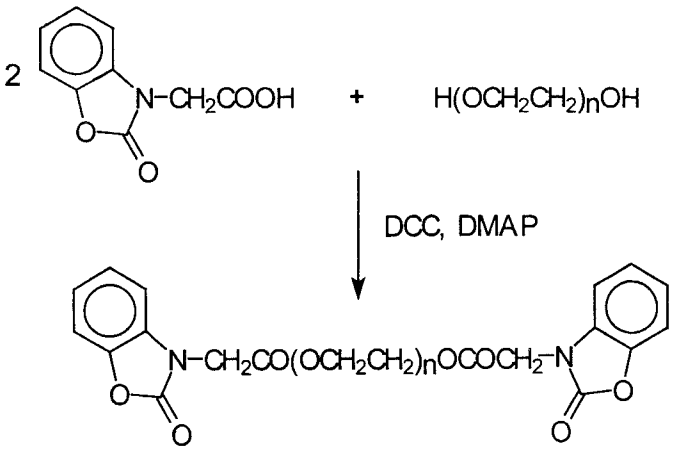
The pH changes in the solutions during complex formation were followed by a Präcitronic type MV 88 pH-meter. The viscosity measurements were performed with an Ubbelohde viscometer at 25°C.

The BOAA derivatives of POEs are denoted as POE.b.

Synthesis of POE.b$_{600\text{-}4000}$ diesters of BOAA

POE.b were prepared by reacting PEGs of molecular weights from 600 Da to 3000 Da with BOAA in DMF-CH_2Cl_2 in the presence of DCC and DMAP similarly to a known procedure [2, 16] according to Scheme 1.

The starting POEs were dried at 40°C under reduced pressure for 2 hours. BOAA (22 mmol) was dissolved in a minimum amount of DMF and CH_2Cl_2 (15 ml) was added. A solution of the corresponding POE (10 mmol) in 20 ml CH_2Cl_2 and a solution of DMAP (2.5 mmol) in 2 ml CH_2Cl_2 were added. After complete



SCHEME 1. Synthesis of poly(oxyethylene)s with (2-benzoxazolon-3-yl)acetyl end-groups (POE.b); n - average number of repeating units (13, 23, 34, 45 or 68).

dissolution at room temperature, DCC (26 mmol) in 10 ml CH_2Cl_2 was added portionwise to the reaction mixture with continuous stirring. After 10-15 minutes, the white precipitate of dicyclohexylurea was formed. The reaction mixture was stirred at room temperature until the disappearance of BOAA (TLC control) and then was filtered. The filtrate was evaporated to dryness. The residue was taken up with cooled acetone and then filtered. The acetone filtrate was precipitated in diethylether at 10°C. The products prepared were purified by repeated precipitation in ether. Yields: 70-84%.

RESULTS AND DISCUSSION

Preparation and Properties of POE Diesters of BOAA

It is known that, in the presence of DCC, esters are obtained under mild conditions and with good yields [16-18]. POE.b are obtained according to Scheme 1; when applying this method, a degree of substitution of 82-92% of the diesters was attained in CH_2Cl_2 containing a small amount of DMF. The obtained diesters, α-(2-benzoxazolon-3-yl)acetyl-ω-(2-benzoxazolon-3-yl-acetoxy) polyoxyethylene (POE.b), were obtained in 70-84% yield.

The molecular weight characteristics of the diesters are summarized in Table 1. At room temperature, $POE.b_{600}$ and $POE.b_{1000}$ are highly viscous liquids.

TABLE 1. Molecular Weights (SEC) and Other Characteristics of POEs and POE.b

Polymer	$\overline{M}_w$	$\overline{M}_n$	$\overline{M}_w/\overline{M}_n$	Esterified groups, (%)[a]	Yield (%)	M.p. (°C)[b]
POE_{600}	520	470	1.11	–		17-23
$POE.b_{600}$	930	900	1.04	88	70	−10
POE_{1000}	960	910	1.06	–		37-40
$POE.b_{1000}$	1320	1280	1.03	92	79	16
POE_{1500}	1500	1440	1.04	–		46-49
$POE.b_{1500}$	1600	1510	1.06	92	80	35
POE_{2000}	1910	1820	1.05	–		50-53
$POE.b_{2000}$	2290	2210	1.04	89	76	42
POE_{3000}	2880	2720	1.06	–		56-59
$POE.b_{3000}$	3240	3100	1.05	82	77	45

[a] *Based on ^{1}H-NMR analyses.* [b] *Based on DSC analyses.*

POE.b of higher molecular weight (1500 Da, 2000 Da and 3000 Da) are solid. Their melting points are 10°C below those of the corresponding unsubstituted POEs. All of them are soluble in water and organic solvents (methanol, ethanol, chlorinated hydrocarbons, acetone, tetrahydrofuran, dimethylsulfoxide). $POE.b_{600}$ is sparingly soluble in water.

SEC analyses showed the absence of unreacted (2-benzoxazolon-3-yl)acetic acid and also that the relatively narrow molecular weight distribution is retained (in the range $\overline{M}_w/\overline{M}_n$ = 1.03-1.11). Functionalization of POEs with (2-benzoxazolon-3-yl)acetyl groups is confirmed by the appearance of intensive UVabsorbance in POE.b.

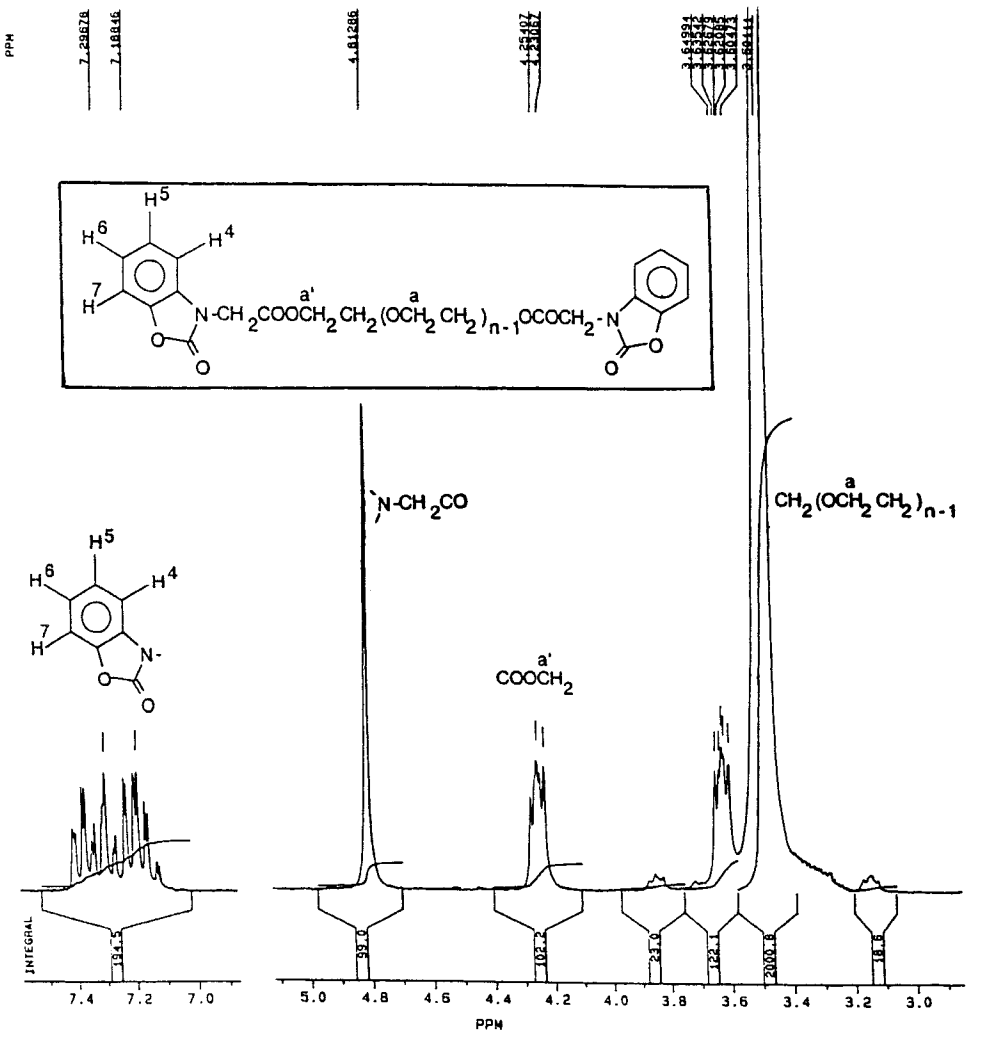


Figure 1. ^{1}H-NMR spectrum of POE.b$_{1000}$, DMSO-d$_6$.

In the IR spectra of the diesters (in $CHCl_3$), an absorption band is observed at 1755 cm^{-1} for ester carbonyl group and a second band at 1790 cm^{-1} for carbonyl group of the benzoxazolone ring. In the spectra of the POE.b no broad band for OH group at 3300-3500 cm^{-1} was recorded.

A typical ^{1}H-NMR spectrum is shown in Figure 1. The formation of an ester bond between BOAA and POE is proved by the appearance of a triplet at 4.24 ppm due to -COOC$\underline{H}_2$ - protons. A broad multiplet is centred at 3.50 ppm for the

protons of methylene groups in polyether chain and a singlet at 4.80 ppm for the protons of the benzoxazolonyl-N-C$\underline{H}_2$ group. In the ^{1}H-NMR spectrum of POE.b$_{1000}$ signals appear for aromatic ring protons at 7.12-7.40 ppm (multiplet). The structure of signals for aromatic protons in DMSO-d_6 for benzazole derivatives shows three multiplets [19, 20]. In the ^{1}H-NMR spectra of PEGs in DMSO-d_6 a triplet at 4.60 ppm due to the protons from the hydroxyl end-groups is observed [21]. This hydroxyl peak does not shift or broaden as in other solvents and disappears under conditions of deuteroexchange. Such a signal is lacking in the ^{1}H-NMR spectra of POE.b derivatives in DMSO-d_6 thus showing that mainly diesters have been obtained.

The structure of the poly(oxyethylene) esters of BOAA and the nature of end-groups were determined also by comparison of ^{13}C-NMR spectroscopic data (in $CDCl_3$) for POE.b$_{1000}$ with those of (2-benzoxazolon-3-yl)acetic acid methyl ester. The following signals were observed in the ^{13}C-NMR spectra of the methyl ester of BOAA: δ(ppm) 43.3 (N-$\underline{C}H_2$-CO), 53.2 (COO$\underline{C}H_3$), 155.4 (N-$\underline{C}$O-O), 168.3 (N-$CH_2\underline{C}OOCH_3$), 109.1, 110.9, 123.8, 124.8, 131.5, 143.6 (aromatic C). The description of the signals for POE.b$_{1000}$ is as follows: δ(ppm) 44.0 (N-$\underline{C}H_2$CO), 156.4 (N-$\underline{C}$O-O), 168.4 (N-$CH_2\underline{C}OOCH_2$), 71.68 ($\underline{C}H_2$O (a)), 69.80 ($\underline{C}$H2O (a')), 66.10 ($\underline{C}H_2$O (a'')), 101.0, 111.5, 124.4, 125.5, 132.2, 144.7 (aromatic C).

Interpolymer Complexes of POE Diesters with Polyacids

It is known that PAA and PMA form polycomplexes with POE in dilute aqueous solutions. Complex formation proceeds by the formation of hydrogen bonds between the oxygen atoms of POE and the hydrogen atoms of the undissociated carboxyl groups in the polyacids. For this reason, the acid-base equilibrium of the system is shifted and pH of the solution increases. Complex formation is accompanied by an abrupt drop in the solution viscosity since the complex particles are rather compact globules. The stability of the polycomplexes depends substantially on the chain length of the low-molecular component POE [22]. Hydrophobic interactions play a significant role in complex formation. We have reported on the interpolymer complex formation between polyacids and poly(oxyethylene)s bearing residues from hydrophobic biologically active compounds as end-groups [3-5, 7]. It was shown that the hydrophobic groups favor the complex formation. The same effect may be expected on attachment of (2-benzoxazolon-3-yl)acetic acid to the POE chains.

The changes in η_i (relative viscosity increment) and pH of mixtures of aqueous solutions of PAA (PMA) with POE.b on the weight ratio [POE.b]/[PAA]([PMA]) are shown in Figures 2 and 3. The viscosity of the solutions of POE.b and PAA (PMA) drops abruptly with the increase in the [POE.b]/[PAA] ([PMA]) ratio, even in the case of POE.b_{600}, where the molecular weight of the POE chain is about an order of magnitude lower than the critical molecular weight for complex formation with PAA and three times lower than that one for complex formation with PMA. This behavior may be explained with the effect of hydrophobic groups in the POE.b molecule, stabilizing the polycomplexes with polyacids.

The dependences discussed have a clear minimum characteristic of the most compact state of the complex globule; the subsequent addition of POE.b does not lead to further interaction. Once the minimum is attained, the added POE.b increases the viscosity. the fact that the higher the molecular weight of POE.b, the higher this increase, suggests that the new portions of POE.b do not interact with the polyacid.

The position of the minimum is also of interest. For the complex with PAA it appears at a POE.b/PAA weight ratio of 3.5-4.0 (Figures 2a and 2b). the POE.b molecular weight affects only slightly the position of the minimum. The equimolar ratio between the two types of monomer units corresponds to the weight ratio [POE.b]:[PAA] = 0.61. It is clear that the most compact polymer globule is formed at a considerably higher weight ratio. Probably, this is an effect of the increased compactness of the complex globule and, consequently, the diffusion of the POE.b molecules into the globules becomes more difficult. To overcome these difficulties, the polybase concentration gradient into and out of the globules should be increased.

Quite different is the situation for the POE.b complex with PMA (Figures 3a and 3b). The minimum position in this case is close to the equimolar ratio of both monomer units and corresponds to the weight ratio [POE.b]:[PMA] = 0.51. It is evident from the results presented in Figures 3a and 3b that for POE.b_{600} and POE.b_{1500} the minimum appears at a [POE.b]:[PMA] weight ratio of 1.0, while for the higher POE.b (POE.b_{2000} and POE.b_{3000}) the minimum weight ratio is 0.3.

A great excess of polybase is required for complex formation with PAA. The difference between the PAA and PMA complex behavior shows once more the considerable contribution of the PMA α-CH_3 group to the increase of the hydrophobic interaction between macromolecules, in comparison to that of PAA.

It should be noted that pH increases with increase of [POE.b]:[PAA] ([PMA]) weight ratio in the weight ratio range where the sharp drop in viscosity is observed (Figures 2a, b and 3a, b).

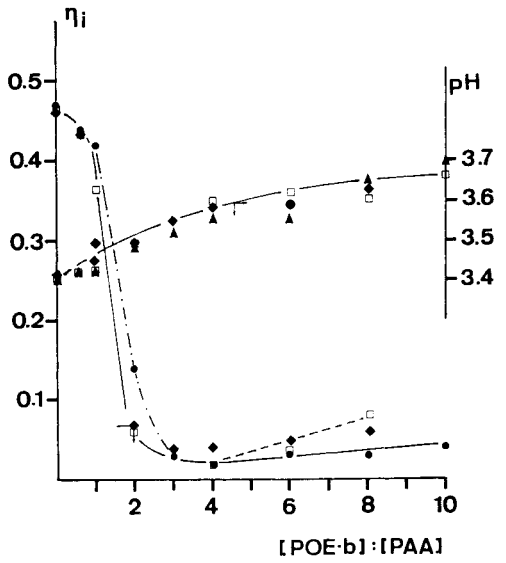


Figure 2a. Dependence of η_i and pH of mixtures of aqueous solutions of POE.b and PAA on the [POE.b]/[PAA] ratio at a fixed concentration of PAA (0.1g/dl, 25°C): (●, Δ) - POE.b_{600}; (◆) - POE.b_{1000}; (□) - POE.b_{1500}.

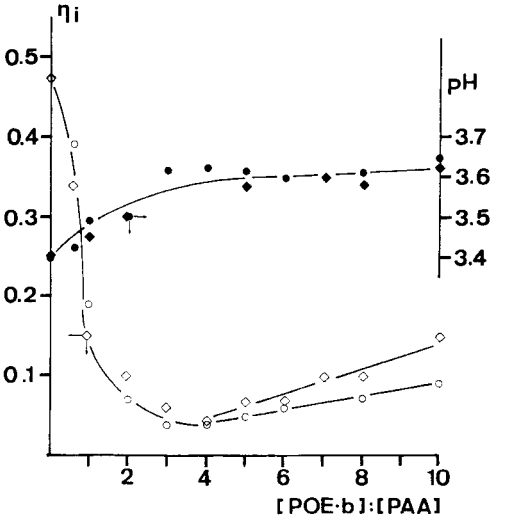


Figure 2b. Dependence of η_i and pH of mixtures of aqueous solutions of POE.b and PAA on the [POE.b]/[PAA] ratio at a fixed concentration of PAA (0.1 g/dl, 25°C): (○, ●) - POE.b_{2000}; (◊, ◆) - POE.b_{3000}.

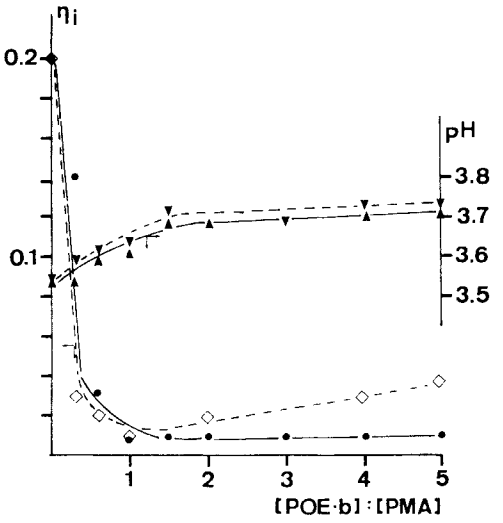


Figure 3a. Dependence of η_i and pH of mixtures of aqueous solutions of POE.b and PMA on the [POE.b]/[PMA] ratio at a fixed concentration of PMA (0.1 g/dl, 25°C); (●, Δ) - POE.b_{600}; (◊, ▽) - POE.b_{1500}.

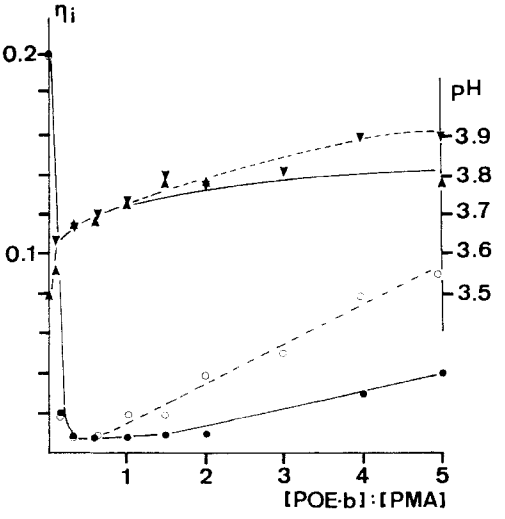


Figure 3b. Dependence of η_i and pH of mixtures of aqueous solutions of POE.b and PMA on the [POE.b]/[PMA] ratio at a fixed concentration of PMA (0.1 g/dl, 25°C); (●, Δ) - POE.b_{2000}; (○, ▽) - POE.b_{3000}.

CONCLUSION

The above data reveal that the presence of BOAA groups in the macromolecules of POE favors the formation of complexes with PAA and PMA. The nonspecific interactions due to the (2-benzoxazolon-3-yl)acetyl groups of POE.b play an important role in the stabilization of the polycomplexes. In the complex of POE with hydrophobic end-groups and polyacids, the end-groups are located in the hydrophobic domains of the complex. It might be expected that this will result in a decrease in the rate of hydrolysis of the ester bonds between BOAA and the polyether chain and also of the ester bond in the benzoxazolon group.

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