# Bisphosphonate Units in the Main Polymer Chain: the First Synthesis

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**ABSTRACT:** Radical copolymerization of tetraethyl vinylidene phosphonate (**B**) with vinyl monomers has been described for the first time. In copolymerization with vinyl acetate (**V**) strictly alternating copolymer was formed even when  $[V]_0/[B]_0$  was equal to 80. In copolymerization with acrylic acid (**A**) copolymers of the general structure  $-[(B)_1A_x)]_n$  were formed. The number of **A** units (*x*) was shown to depend on the  $[A]_0/[B]_0$  ratio in the monomers feed. The reactivity ratio  $r_A$  was determined as equal to 2.1 and on this basis, the distribution of *x* as

**INTRODUCTION** Various derivatives of bisphosphonates are used as biologically active compounds. This is related to their high ability to complex metal ions and particularly calcium cations  $(Ca^{+2})$ .<sup>1</sup> The presence of four P-OH groups on one carbon atom, namely  $=C[P(O)(OH)_2]_2$ , provides their unusual properties. For this reason, several well-known drugs used for fighting osteoporosis are derivatives of bisphosphonic esters and (mostly) bisphosphonic acid.<sup>2,3</sup>

Bisphosphonates are chemically stable analogs of inorganic pyrophosphates and are stable toward enzymatic breakdown. Related compounds are also being used as coatings when stronger fixation of, for example, screws to the surrounding bones is required.<sup>4</sup> In our preliminary paper, it has also been shown that the related compounds may be used for CaCO<sub>3</sub> modification and attachment of polylactide.<sup>5</sup> Similar approach has been described recently for low-molecularmass bisphosphonates.<sup>6</sup>

There are no (at least in the open literature) reports on an attempt to prepare linear polymers with bisphosphonates as repeating units in the main chain.

However, it has to be noted that polymers with bisphosphonate units in the side chains have already been known. Recently published paper by Kopeček a. o. describes fixation of bisphosphonate derivatives, to the N-(2-hydroxypropyl)methacrylamide copolymer and formation this way the corresponding bioactive conjugate.<sup>7</sup>

This article is the first one describing syntheses of macromolecules having bisphosphonate units in the main chain. a function of  $[\mathbf{A}]_0/[\mathbf{B}]_0$  was found. Bisphosphonic units were deblocked and the corresponding polyacids were analyzed by NMR spectra.  $M_n > 0.5 \times 10^6$  were measured by SEC for copolymers of **B** with **A**. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 50: 3030–3038, 2012

**KEYWORDS**: copolymerization; heteroatom-containing polymers; microstructure; radical polymerization; water-soluble polymers

Attempts to homopolymerize esters of bisphosphonic acids were unsuccessful, most probably due to the large size of the monomer molecules. This inability has also been earlier observed by Alexandratos, who prepared only a series of insoluble polymers with divinylbenzene as the ion exchangers.<sup>8</sup>

However, copolymerization with properly chosen comonomers allowed preparation of alternating and random copolymers. The first comonomer that has been tested in this work has been vinyl acetate (V). Hydrolysis of the copolymer provided chains with bisphosphonic units and free hydroxyl groups that could be used for further functionalization. This process and preparation of copolymer with bisphosphonic acid units and units of alcohol are described, together with description of copolymers with acrylic acid (A), providing copolymers with carboxylic and bisphosphonic acids as repeating units.

#### **EXPERIMENTAL**

#### Materials

Tetraethyl vinylidene phosphonate (**B**) was synthesized according to the procedure described in details by Degenhardt and Burdsall.<sup>9</sup> The starting tetraethyl methylene bisphosphonate was purchased from Aldrich or prepared by reaction of  $CH_2Br_2$  with  $P(OEt)_3$ .

Vinyl acetate (**V**) (Aldrich) was distilled before use. Fraction boiling at 72 °C was collected. Acrylic acid (**A**) (Aldrich) was distilled before use. Fraction boiling at 141 °C was collected.

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# Copolymerization of Tetraethyl Vinylidene Phosphonate (B) with Vinyl Acetate (V)

## Example for $[B]_0/[V]_0 = 1.06/1$

1.04 g  $(3.47 \times 10^{-3} \text{ mol})$  of **B**, 0.28 g  $(3.26 \times 10^{-3} \text{ mol})$  of **V**, and 0.026 g  $(1.6 \times 10^{-4} \text{ mol})$  of azoisobutyronitrile (AIBN) were placed in the glass ampoule and connected to the vacuum line. The mixture was degassed six times by freezing and melting under reduced pressure and finally sealed. The reaction mixture was heated at 80 °C during the desired time. Copolymer was separated from the mixture by ultrafiltration using membrane cut off 500.

# Copolymerization of Tetraethyl Vinylidene Phosphonate (B) with Acrylic Acid (A)

# *Example for* $[B]_0/[A]_0 = 2.28/1$

Copolymerization of **B** with **A** and separation of the final product were conducted in the same way as described for copolymerization of **B** with **V**. The following amounts of reagents were used: **B** = 1.39 g ( $4.63 \times 10^{-3}$  mol), **A** = 0.76 g ( $1.05 \times 10^{-2}$  mol), and AIBN = 0.04 g ( $2.44 \times 10^{-3}$  mol).

# Hydrolysis (dealkylation) of Copolymers

# Hydrolyses of Copolymers B-V as well as B-A were Carried Out in the Same Way

Example: 1.0 g of copolymer **B-V** was dissolved in 50 mL of 5 M hydrochloric acid. The mixture was refluxed during 5 h. After that time, the acetic groups of **V** units were completely removed and ethyl groups from bisphosphonate units were hydrolyzed in 98% (according to <sup>1</sup>H NMR spectra). Copolymer was purified by ultrafiltration using membrane cut off 500.

# Measurements

# NMR Spectra

The  $^1\text{H}$  (200 MHz),  $^{13}\text{C}$  (50 MHz), and  $^{31}\text{P}$  (81 MHz) NMR spectra were recorded at 25 °C on a Bruker AC200 spectrometer. Standard acquisition parameters were applied.  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra for quantitative estimation of various structures in the product were recorded with inverse gated proton decoupling and time delay between pulses equal to 30 s.

#### **MALDI-TOF**

Mass spectrometric measurements were performed using a Voyager-Elite (PerSeptive Biosystems) time-of-flight instrument equipped with a pulsed N<sub>2</sub> laser (337 nm, 4-ns pulse width) and time-delayed extraction ion source. An accelerating voltage of 20 kV was applied. Mass spectra were recorded in the linear and reflector mode. The matrix, 2,5-dihydroxybenzoic acid (DHB), Li<sup>+</sup> was used.

#### Molar Mass Determination

SEC chromatography with triple detection was carried out on the chromatograph Knauer K-501 high performance liquid chromatography (HPLC) pump with LDC refractive index (RI) detector and Viscotek T60A dual detector (right angle laser light scattering, at  $\lambda = 670$  nm and differential viscometer). Three Suprema columns (30 + 100 + 3000 Å; 8 × 300 mm<sup>2</sup>; Polymer Service Standard) were used in a series. Aqueous solution of NaN<sub>3</sub> (0.1%) was degassed (4-Channel Degasser; K-5004, Knauer) and used as a mobile phase at the flow rate of 1.0 mL/min. Samples (concentration of polymers:  $\sim$ 7 mg/mL) were filtered through 0.2  $\mu$ m pore size membrane filters. Injection volumes of the sample solutions were 100  $\mu$ L. TriSEC software (Viscotek) was used to treat the data.

## **RESULTS AND DISCUSSIONS**

#### Monomer Synthesis and Monomer NMR Spectra

Starting monomer: tetraethyl vinylidene phosphonate (B) was prepared according to the known procedure<sup>9</sup> in the following steps, shown in Scheme 1.

Monomer—bisphosphonate (**B**)—prepared according to Scheme 1 was further purified by fractional distillation at 102 °C/0.2 mmHg. The final purity was established by <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR. We are showing these spectra, as this is the first time in the polymer literature and could be useful for other researchers. Besides, particularly the <sup>31</sup>P NMR spectrum, indicate the level of **B** purity. The corresponding assignments of peaks are given in the Figures 1–3.

The NMR spectra are simple and self-explanatory. It may, however, be added that four lines from protons (a) at the double bond in **B** are due to the geminal AB system. The nonequivalence comes from cis- and trans-interactions with P atoms. It is in agreement with a generated spectrum, according to ACD/HNMR DB program (v. 6.12).

As it follows from the <sup>31</sup>P NMR spectrum (Fig. 3), there is approximately 2.0% of a major impurity with a chemical shift at 19.5 ppm. Most probably this is the starting compound **1**, for which the known chemical shift is equal to 19.0 ppm.<sup>10</sup> These values are close enough when difference in conditions of the <sup>31</sup>P NMR measurements are taken into the account. There are also a few smaller signals; attempts to remove completely the major and other impurities (at least to the level of not being seen at the <sup>31</sup>P NMR spectrum) were not successful. The difference in the boiling points of **1** and **B** is too small and thermal stability of **B** does not permit using some other preparative methods. Moreover, handling **B** on the high vacuum line was also not possible, due to its low vapor pressure.

Copolymerization of B was conducted with vinyl acetate (V) and acrylic acid (A). Both in bulk. The choice of comonomers



**SCHEME 1** Synthetic route of tetraethyl vinylidene phosphonate (**B**).



ARTICLE



**FIGURE 1** The <sup>1</sup>H NMR spectrum (in  $C_6D_6$ ) of the tetraethyl vinylidene phosphonate (**B**).

was based on the assumption, already indicated in Introduction section, that finally copolymer with V could be obtained (after hydrolysis) with hydroxyl groups containing units and copolymer with A with carboxylic acid units.

#### **Copolymerization Conditions**

Relatively high molar mass copolymers have been obtained in radical polymerization.

Typical radical copolymerizations were conducted at 80  $^\circ$ C in ampoules filled with both comonomers and initiator and sealed in vacuum, after degassing. AIBN was used as initiator.

#### Copolymerization of B with V

Copolymerization of monomers  $\boldsymbol{B}$  and  $\boldsymbol{V}$  can be described with Scheme 2.



**FIGURE 2** The  ${}^{13}C{}^{1}H$  NMR spectrum of the tetraethyl vinylidene phosphonate (**B**).



**FIGURE 3** The  ${}^{31}P{}^{1}H$  NMR spectrum of the tetraethyl vinylidene phosphonate (**B**).

Preliminary results (no kinetic studies were performed) indicated that in this copolymerization close to complete monomers conversion takes  $\sim$ 30 h at 80 °C (when  $\sim$ 1:1 comonomers ratio was used).

In copolymerization with  $[V]_0/[B]_0 = 1$  (f = 1.0), conducted in bulk with  $[AIBN]_0 = 0.05$  mol % (for both monomers), at 80 °C, samples of the polymerization mixture taken at various times of reaction and were analyzed by <sup>1</sup>H and <sup>31</sup>P NMR. After 3, 4, and 8 h of reaction (conversions 68, 74, and 81%, respectively) the ratio of the corresponding polymer units was close to 1:1 within ~10% of uncertainty. Results are shown in Figure 4.

The 1:1 monomer ratio of comonomers was used in these experiments after establishing that up to 80:1  $[V]_0/[B]_0$  ratio (i.e., f = 80) the alternating copolymer is formed. At this ratio, the <sup>1</sup>H NMR data and ELEM. ANAL indicate formation of alternating copolymer, like it is shown in matrix-assisted laser desorption/ionization time of flight (MALD-TOFI)-ms (Fig. 5) for  $[V]_0/[B]_0 = 1.0$  ratio. Therefore, the 1:1 ratio secured that after the complete conversion of **B** the copolymer would not be contaminated by **V** homopolymer. This is seen indeed in Figure 5 of the MALDI-TOF results for the copolymer prepared at practically full conversion.

Two main populations of signals are present in the MALDI-TOF spectrum (Fig. 5). To the first one, marked in gray, macromolecules I-(b-v)<sub>n</sub>-b' (structure **3**) see Scheme 3 can be assigned, whereas the second generation of peaks, indicated with the black bars, could be described as related to the structures, I-v-(b-v)<sub>n</sub>-b' (**5**) and/or I-(b-v)<sub>n</sub>-b-v' (**6**). Structures I-(bv)<sub>n</sub>-(bv<sub>2</sub>)<sub>1</sub>-(bv)<sub>m</sub>-b' (**4**) have identical m/z. These macromolecules have to contain in one (and only one) unit two consecutive -v- units (v<sub>2</sub>). This may happen, even if there are practically no macromolecules with -v<sub>3</sub>- units. We could not distinguish between the structures **4**, **5**, and **6** (NMR spectra could not be of help). Thus either one of these or mixtures of **4**, **5**, and **6** should be present. Structure **5** 



SCHEME 2 Copolymerization of B with vinyl acetate (V).

requires that initiation involves **V**, although reactivity of **B** toward radicals looks to be higher. Structure **6** requires radical transfer from v' (end group of **V**). It is difficult to accept this assumption, as radical polymerization of **V** is known to lead to high polymers. Besides, there is no population found of macromolecules started and ended with **V**.

The structure of the end-groups as shown in schemes (unsaturated) might indicate that some of the material chains are terminated by disproportionation. Disproportionation would require, however, the presence of an equal proportion of macromolecules with saturated end-groups. These are absent. Thus, termination of material chains most likely results from chain transfer. As the polymerization was found at the screening experiments to be rather slow, relatively high concentration of AIBN was used (cf. Experimental section; [AIBN]<sub>0</sub> usually ~0.05 mol % of the monomers used). Transfer to initiator may also take place, although no attempt has been made to find the resulting low molar mass compounds.

In some MALDI-TOF spectra macromolecules initiated by  $H^{\bullet}$  addition to **B** monomer and of the structure **7** are observed (Scheme 4).

This would mean transfer to  ${\bf B}$  monomer, starting a new material chain.

Because of the uncertainty of the chemistry of transfer, no attempt was made to determine the transfer constants. If the transfer were exclusively to monomer, then the transfer constant could be estimated from the polymerization degree and  $k_{\rm p}/k_{\rm tr} = 5$  would result.



FIGURE 4 Conversion of comonomers (B and V) as a function of time.

The NMR spectra of the **B-V** copolymers are in agreement with the observed alternating structure as it follows from the conversion studies. The <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectra of copolymers are shown in Figures 6 and 7, in which the corresponding assignments, chemical shifts, and integrations are given. Integration of signals in the <sup>1</sup>H NMR spectrum is indeed in agreement with the 1:1 ratio of -v- and -b- repeating units. If, as postulated above, some macromolecules would have indeed one  $-v_2$ - unit per macromolecule, this would be within an experimental error of the NMR integrations.

Eight protons in  $CH_2$  from -b- units (5) integrated as 8.32 and one proton from -v- units (4) integrates as 1.00.

The <sup>13</sup>C NMR spectrum has not been quantitatively analyzed.

## Copolymerization of B with Acrylic Acid (A)

Copolymerization of **B** with **A** gives copolymers of the general structure  $-[(b)_1-(a)_p]_n$ - where "p" depends on the starting ratio  $[\mathbf{B}]_0/[\mathbf{A}]_0$ . This difference between copolymerization of **B** with **V** or **A** could be related to the differences of  $k_p$  of homopropagations of **V** and **A** although it stems more directly from a difference between the rates of addition of **B** and the rates of homopropagation of the corresponding comonomer ( $k_{2B}/k_{22}$ , where 2 stands for a comonomer). Indeed, when during copolymerization ...-v° radical or ...-a°



**FIGURE 5** MALDI-TOF spectrum of **B-V** copolymer. Populations of macromolecules:  $I-(bv)_n-b'$  (3),  $I-v-(bv)_n-b'$  (5) and  $I-(bv)_n-b-v'$  (6)—signals 3 marked in gray, 4, 5, and 6 in black; (-b- and -v- mean repeating units of **B** and **V** monomers). Conditions: matrix DHB, positive ionization with Li<sup>+</sup>. Further explanation in the text.



SCHEME 3 Hypothetical structures of macromolecules (3, 4, 5, and 6) in B-V copolymer.

radical appears than there is a choice of homopropagation or cross propagation. The  $r_{\rm b}$  and  $r_{\rm v}$  are both equal to zero, although for different reasons  $r_{\rm b} = 0$ , since  $k_{\rm bB}$  (being rate constant of addition of **B** to its radical ...-b<sup>•</sup>) equals to zero. On the other hand  $r_{\rm v} = 0$ , since  $r_{\rm v} = k_{\rm vV}/k_{\rm vB}$  and apparently  $k_{\rm vB} \gg k_{\rm vV}$ . The donor-acceptor complex formation as responsible for alternation is not taken into account, since (*vide infra*) neither **A** nor its esters (unpublished results) give alternating copolymers with **B**. In copolymerization of **B** with **A**  $r_{\rm b} = 0$  again, by the same token as in copolymerization with **V**. Thus, if  $r_{\rm aA} > 0$ , then it means that  $k_{\rm aA} > k_{\rm aB}$ (whereas  $k_{\rm vV} \ll k_{\rm vB}$ ). Whether electronic or steric effects prevail is not clear. It could not be excluded that in the studied system rate constant of **A** homopolymerization is much higher than the known  $k_{aA}$ , mostly measured in water at pH > 7, when **A** aggregates may be broken. If aggregates persist, than the effective rate of propagation may be much



**SCHEME 4** One of the structures (7) of **B-V** copolymer initiated by H<sup>•</sup>.



**FIGURE 6** The  ${}^{1}H$  NMR spectrum (in D<sub>2</sub>O) of the **B-V** copolymer.

higher than in their absence. Comparison of homopropagation **A** with **V** is not easy on the basis of the available data, however, the rate of addition of  $\boldsymbol{A}$  to a model radical is at least  $10^2$  times higher (in acetonitrile solvent) than the rate of addition of  $\mathbf{V}^{11}$ . This difference is also apparent from the known data of copolymerization of **V** and **A**, namely  $k_{aA}/k_{aV} =$ 8 whereas  $k_{\rm vv}/k_{\rm vA} = 0.2.^{11}$ 

The composition of B-A copolymers was determined from the <sup>31</sup>P NMR spectrum recorded with external standard (tbutylphosphonic acid,  $\delta = 29.5$  ppm). On the basis of the P content in the sample, the average composition of copolymer has been determined. Results have been compared with data calculated from the <sup>1</sup>H NMR spectrum, shown in Figure 8 (assignments are given in the Figure).

The copolymer composition from the <sup>1</sup>H NMR spectrum is based on integrations of protons (5) (8 units, integration equal



FIGURE 7 The  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum (in  $C_6D_6)$  of the B-V copolymer registered at the standard conditions.



C2H5O OCH2CH

to 1) and protons (1), (3), (4), and (6). The contributions of protons (1) and (6) are known from integration of protons (5). Then integration of protons (3) and (4) (coming from unit -a-) is determined. Thus, from Figure 8 the average ratio of units -a- and -b- equals to 16.3. This ratio from the <sup>31</sup>P NMR spectrum (recorded with external standard) equals to 17.0.

The  ${}^{31}P{}^{1}H$  NMR spectrum of purified by ultrafiltration B-A copolymer is given in Figure 9.

In the  ${}^{31}P{}^{1}H$  NMR spectrum of the copolymer of **B** and **A** there are two peaks: a multiplet and apparently singlet. Always, independently on conversion, the integrated ratio of these peaks is close to 1:1 (actually 1.25 in Fig. 9). Most probably one half of the -b- units interact by H-bonding with -a- units and becomes less mobile than the other half that would not have the -a- partner. This is true independently of



FIGURE 9 The <sup>31</sup>P{<sup>1</sup>H} NMR spectrum (in D<sub>2</sub>O) of the B-A copolymer.

the unit's placement and their number, although the multiplicity of the peak at 27 ppm may indicate some more subtle longer range interaction.

# Determination of the Reactivity Ratios in the B-A Copolymerization

Copolymerization was conducted at 80 °C in bulk and after several screening experiments time needed to have conversion of B monomer close to 5% was established. Conversion of A, which is more reactive (consumed faster) was a function of the  $[A]_0/[B]_0$  ratio. After the required time, the copolymer/monomer mixture was cooled down to the room temperature and dissolved in  $D_2O$  or dimethyl sulfoxide (DMSO)-d<sub>6</sub>. As the double bonds of **A** and **B** are well separated in <sup>1</sup>H NMR, conversion of a given monomer was established by comparing the integrals of the  $CH_3$  protons, taken as an internal standard, (do not change) and of the integrals of the double bond of the A or B, respectively. Figure 10 gives the <sup>1</sup>H NMR spectra of the starting monomers mixture (10a) and the monomer-polymer mixture after a few percent of conversion (10b); assignments of signals are given directly on the spectrum.



**FIGURE 10** The <sup>1</sup>H NMR spectra of: (a) starting reaction mixture (spectrum in  $C_6D_6$ ) and (b) after about 5% of conversion of monomer **B** (spectrum in  $D_2O$ ). Some differences in the chemical shifts are due to different solvents used.



**FIGURE 11** Determination of the reactivity ratio  $r_2$  according to the Fineman–Ross method. As it could be expected the slope (i.e.,  $r_1$ ) is equal to 0 and  $r_2 = 2.1 \pm 0.2$ .

The copolymer composition (*F*) and the monomer composition (*f*) were thus determined for several different *f*. Results were analyzed according to the Fineman-Ross equation and in Figure 11 the plot of f(F-1)/F as a function of  $f^2/F$  is shown.

# Determination of the Sequence Distribution<sup>11</sup>

We determined the sequence distributions for the low monomer conversions from experiments described in the previous section. Typical sequence distribution of **A** units (**B** is always present as unimer) for low conversions is shown in Figure 12.

#### **Dealkylation and Hydrolysis of Copolymers**

In dealkylation of the esters of phosphonic acid usually trimethylbromosilane (TMBS) is used. Preliminary experiments have, however, shown that removal of the ester groups in copolymers **B-V** as well as **B-A** does not go to completion



**FIGURE 12** The sequence distribution of **A** units in **B-A** copolymer for various starting comonomers ratios for the beginning of conversion. Solid lines -  $[A]_0/[B]_0 = 1.08$ ; dashed lines -  $[A]_0/[B]_0 = 2.96$ ; dotted lines -  $[A]_0/[B]_0 = 5.17$ .



SCHEME 5 Hydrolysis of B-V copolymer.

when TMBS is used. Therefore, much more powerful (and drastic) method was used, namely concentrated water solution of HCl (5M, i.e., 18 wt %). This method is also of preference, since when copolymer B-V is treated in this simple way, then it was observed that dealkylation proceeds simultaneously with hydrolysis of the -v- unit to the vinyl alcohol unit (Scheme 5).

After 2 h almost complete dealkylation and hydrolysis were attained, as it could be judged from the  $^{13}C\{^{1}H\}$  NMR spectra, shown in Figure 13(a,b). Integration of the respective signals in the  $^{1}H$  NMR spectrum gives  ${\sim}4\%$  of the P-OCH\_2CH\_3 groups left in the product.

Hydrolysis of B-A copolymer was conducted at the same conditions as for B-V copolymer. Progress of reaction was



**FIGURE 13** <sup>13</sup>C{<sup>1</sup>H} NMR spectra of the **B-V** copolymer: (a) before (in  $C_6D_6$ ) and (b) after hydrolysis (in  $D_2O$ ).



**FIGURE 14** The <sup>1</sup>H NMR spectra (in  $D_2O$ ) of **B-A** copolymer: (a) before hydrolysis, (b) after hydrolysis. Hydrolysis conditions: 5 M HCl, 100 °C, 2 h.

controlled by <sup>1</sup>H NMR. After 2 h, hydrolysis was almost completed. Results are shown in Figure 14(a,b). As it is seen signals from the ethyl groups (5, 6) almost disappeared.

#### Molar Masses of B-A Copolymers

The molar masses of **B-A** copolymers (after hydrolysis and conversion into the Na salts) were measured with a Viscotek triple-detection apparatus with TriSEC software. Column was calibrated on the poly(acrylic acid) standards. 0.1% NaN<sub>3</sub> aqueous solution was used as the mobile phase. In Figure 15, the size-exclusion chromatography (SEC) traces with RI, viscosity, and multiple angle laser light scattering (MALLS) detectors are given. Four samples were analyzed with molar masses 79.6  $\times$  10<sup>3</sup> up to 876  $\times$  10<sup>3</sup> g mol<sup>-1</sup>.

It is remarkable that in **B-V** copolymers only low molar masses products have been obtained whereas in **B-A** copolymers with  $M_n$  approaching  $10^6$  were prepared. This results from differences in reactivities of **V** and **A** monomers toward radicals, as indicated above. Thus, in copolymerization of **V** and **A** (where **V** is  $M_1$ ),  $r_1 = 0.21$  and  $r_2 = 8.7$ . Therefore, in copolymerization of **B** and **V**, the rate of addition of **V** to the radical of the -b- unit is not sufficient to block the H<sup>•</sup> transfer. It is not the case of the much more reactive monomer **A** that is not allowing the H<sup>•</sup> transfer to lower the copolymer molar masses, blocking the ...-b<sup>•</sup> radicals before H<sup>•</sup> transfer would take place. The molar masses do depend on the  $[A]_0/[B]_0$ 

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**FIGURE 15** The SEC traces of the hydrolyzed **B-A** copolymer of  $M_{\rm n} = 2.84 \times 10^5$  (sodium salt), recorded with Viscotek triple-detection apparatus.

ratio, respectively. The  $[\mathbf{A}]_0/[\mathbf{B}]_0$  ratios and  $M_n$  are given in this order: for example, 3.22:79,600; 4.15:284,000; 10:876,400. Obviously, due to the statistical character of these processes there is a certain inevitable (small) proportion of this transfer, although not visible in SEC.

# CONCLUSIONS

For the first time, polymers with bisphosphonate units in the chains were prepared. Homopolymerization of the monomer, tetraethyl vinylidene phosphonate, does not take place, whereas radical copolymerization with vinyl acetate gives mostly alternating copolymers. Copolymerization with acrylic acid gives high-molar-mass copolymers ( $M_n$  up to  $8.5 \times 10^5$  according to SEC with poly(acrylic acid standards) with a number of acrylic acid units (flanked by bisphosphonate units) depending on the [acrylic acid]<sub>0</sub>/[bisphosphonate]<sub>0</sub>

comonomers ratio. Hydrolysis of the starting copolymers gives final copolymers with reactive groups in the backbones: phosphonic acids and hydroxyl groups (copolymers with vinyl acetate) or phosphonic acids and carboxylic groups (copolymer with acrylic acid).

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#### **REFERENCES AND NOTES**

1 Suzuki, S.; Hayakawa, T.; Kamasaki, N.; Okada, H.; Yamamoto, H. Int. J. Oral-Med. Sci. 2008, 7, 45–49.

**2** Abdou, W. A.; Shaddy, A. A. In Issue 5<sup>th</sup> Eurasian Conference on Heterocyclic Chemistry, ARKIVOC, ARKAT USA, Inc. **2009**, (ix); pp 143–182.

3 Graham, R.; Russel, G. Ann. NY Acad. Sci. 2006 1068, 367– 401.

**4** Wermelin, K.; Suska, F.; Tengwall, P.; Thomsen, P.; Aspenberg, P. *Bone* **2008**, *42*, 365–371.

**5** Kaluzynski, K.; Pretula, J. Polymers for Advanced Technologies, Lodz, Poland, Oct 2–5, **2011**; Book of Abstracts, P-05. Available at: http://www.pat2011.pl/index.php/pat/pat.

6 Chen, J.; Chen, W.; Deng, Ch.; Meng, F.; Zhong, Z. J. Polym. Sci. Part A: Polym. Chem. 2011, 49, 4379–4386.

**7** Pan, H.; Sima, M.; Kopečkova, P.; Wu, K.; Gao, S.; Liu, J.; Wang, D.; Miller, S. C.; Kopeček, J. *Mol. Pharm.* **2008**, *5*, 548–558.

8 Alexandratos, S. D.; Trochimczuk, A. W.; Crick, D. W.; Horwitz, E. Ph.; Gatrone, R. C. Chiarizia, R. *Macromolecules* **1996**, *29*, 1021–1026.

9 Degenhardt, Ch. R.; Burdsall, D. C. J. Org. Chem. 1986, 51, 3488–3490.

**10** Moedritzer, K.; Maier, L.; Groenweghe, L. C. D. *J. Chem. Eng. Data* **1962**, *7*, 307–310.

**11** Odian, G. In Principles of Polymerization, 4th ed.; Wiley: NY, **2004**; Chapter 6, pp 464–543.