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Oligomerisation of hydroxymethacrylates via Michael-type addition

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Abstract

Attempts to conduct step-growth addition polymerisation of monomethacrylates of oligoethylene glycols via Michael-type addition of hydroxyl groups to carbon–carbon double bonds are presented. In the presence of several basic, nucleophilic and acidic reagents, disproportionation to corresponding glycols and dimethacrylates has been observed while some of them were found to initiate oligomerisation according to afore-said mechanism. Optimal reaction conditions have been established. The most effective initiators, i.e. potassium *tert*-butoxide and sodium hydride were selected to obtain the series of oligomers. The products were characterised by ^{1}H NMR, GPC and ESI-MS to confirm oligo(ether–ester) structure and to estimate molecular weight. The latter appeared to be in order of one thousand.

Keywords: Monomethacrylates of oligoethylene glycols; Michael-type addition; Oligo(ether–ester)

1. Introduction

Polymers derived from monomethacrylates of oligoethylene glycols (OEGMMA, Scheme 1) have numerous applications as biocompatible hydrogels. Especially those prepared from monomethacrylate of ethylene glycol (2-hydroxyethyl methacrylate, HEMA) have a great importance and are widely employed in biomedical field, e.g. contact lenses, dental monomers and controlled drug delivery systems [1,2].

Formation of the polymers above proceeds exclusively via chain polymerisation of methacrylate carbon–carbon double bonds. This paper reports on another way of polymerisation (or at least oligomerisation) of hydroxymethacrylates, i.e. via step-growth addition of the hydroxy group to the methacrylic double bond to form oligo(ether–ester)s as shown in Scheme 2. We previously have found that such a process, in fact predominantly dimerisation, accompanies transesterification of oligoethylene glycols by methacrylates in the presence of potassium carbonate [3].

The reactions as above proceed according to the mechanism known in organic chemistry as Michael-type hydro-alkoxy addition [4]. Oligomerisation of hydroxyacrylates [5] and syntheses of hyperbranched systems from dihydroxyacrylates [6,7], both involving this mechanism, were reported. Michael chemistry was used to prepare bismethacrylate monomers and macromonomers bearing pendant alkoxysilane groups [8,9]. Due to difference in charge density distribution, methacrylates are much less susceptible acceptors to nucleophilic addition when compared with acrylates [10]. That might be a reason for which no data on polymerisation of hydroxymethacrylates in such a way has been reported so far. In this paper, we present our attempts to obtain oligo(ether–ester)s from monomethacrylates of oligoethylene glycols using Michael addition chemistry.

2. Experimental

2.1. Materials

HEMA (2-hydroxyethyl methacrylate, Sigma) was dried over anhydrous $MgSO_4$. Monomethacrylates of di-, tri- and tetraethylene glycols (DEGMMA, TEGMMA, TTEGMMA, respectively) were synthesised as described in a previous paper [3]. NaH (Aldrich)-suspension in mineral oil was washed several times with dry tetrahydrofurane and dried under reduced pressure. KOH and K_2CO_3 (POCh), DBU (1,8-diazabicycl[5.4.0]undec-7-ene,

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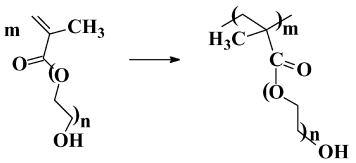


n = 1 HEMA
n = 2 DEGMMA
n = 3 TEGMMA
n = 4 TTEGMMA

Scheme 1.

Aldrich), *t*-BuOK (potassium *tert*-butoxide, Aldrich), PPh_3 (triphenylphosphine, Aldrich), *p*-TsOH (*p*-toluenesulfonic acid, POCh), H_2SO_4 (POCh) and PTZ (phenothiazine, Aldrich) were used as received. Solvents and other auxiliary chemicals were of commercial grade.

2.2. Oligomerisation

The reactions were conducted in bulk under dry nitrogen. The monomer/initiator ratio amounted to 20:1. PTZ (0,15% by weight) was added to prevent free radical polymerisation of double bonds. The reaction mixtures were stirred magnetically for 2 h at the constant temperature. The latter was selected from 25 to 150 °C range and optimised for each catalyst basing on conversion of double bonds measured at this stage. Some selected mixtures were then left to stand for few days at room temperature.

2.3. Separation of oligo(ether–ester)s

The crude reaction mixtures were neutralised by 1% HCl and extracted by $CHCl_3$. In the case of oligomers of HEMA, DEGMMA and TEGMMA the extract was washed few times with water, dried over anhydrous $MgSO_4$ and filtered. The chloroform was then removed under reduced pressure with a rotary evaporator. The residue was washed repeatedly with hexane and dried under vacuum.

Since oligo(TTEGMMA) appeared to be water-soluble, the chloroform extract was just dried and filtered. After evaporation of the solvent, the crude product was precipitated twice in THF/hexane mixture and dried under vacuum.

The final products were obtained with the yield of ca 50% and appeared to be transparent, pale yellow, resinous substances.

2.4. ^1H NMR measurements

^1H NMR spectra were recorded with the aid of UNITY/*INOVA* 300 MHz spectrometer (Varian) using $CDCl_3$ as a solvent and TMS as an internal reference.

2.5. GPC analysis

Gel permeation chromatography measurements were performed in THF (1 ml/min) at 30 °C using Knauer chromatograph with RI detector and column set: 2 × Plgel Mixed-C and 1 × Plgel 100 Å. Molecular weights and polydispersity indexes were determined using narrow molecular weight polystyrene standards calibration.

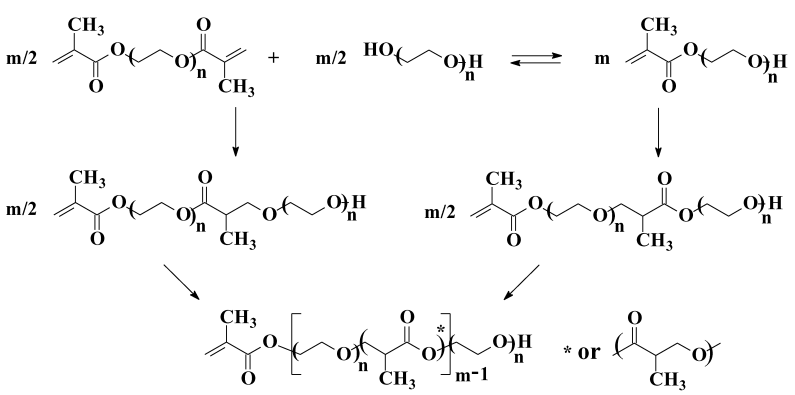
2.6. ESI-MS experiments

Electrospray tandem mass spectrometric analysis (ESI-MS) was performed with a Finnigan LCQ ion trap mass spectrometer (Finnigan, San Jose, CA, USA). The samples were dissolved in methanol (1.0 mg/ml) and solutions were introduced into the ESI source by continuous infusion by means of the instrument syringe pump at a rate of 3 μl/min. The ESI source was operated at 4.25 kV and the capillary heater was set to 200 °C.

3. Results and discussion

3.1. Selection of initiating system and reaction's conditions

As previously [3], we have monitored the course of the reactions with the aid of ^1H NMR spectroscopy. From among hydroxymethacrylates investigated (Scheme 1), HEMA and products of its transformations exhibit least



Scheme 2.

Table 1
^{1}H NMR based conversion values after 2 h for HEMA disproportionation/oligomerisation reaction

Initiator/catalyst	The optimal temperature (°C)	α_{disp}	α_{tot}	F_{add}
K_2CO_3	150	0.36	0.65	0.15
KOH	150	0.42	0.45	0.01
DBU	120	0.40	0.58	0.07
t-BuOK	100	0.20	0.78	0.35
NaH	80	0.20	0.80	0.37
PPh_3	85	0.33	0.33	0.00
p-TsOH	150	0.22	0.69	0.18
H_2SO_4	150	0.23	0.85	0.15

complex spectra and therefore we chose this monomer to select a best initiating system and optimal reaction's conditions.

In the presence of any nucleophilic, basic or acidic catalysts specified in Table 1 HEMA undergoes fast, reversible disproportionation to ethylene glycol (EG) and corresponding dimethacrylate (EGDMA), which is consistent with the literature data [11]. This is visualised in the oxyethylene region of ^{1}H NMR spectrum as shown in Fig. 1; besides two triplets of HEMA at $\delta = 3.87$ and $\delta = 4.29$ ppm, the singlets of EGDMA and EG formed appear at $\delta = 4.40$ and $\delta = 3.70$ ppm, respectively.

Some of the species acting as catalysts in HEMA disproportionation ⇆ transesterification reaction appeared to initiate oligomerisation via Michael-type addition according to Scheme 2. The latter process appears in conversion of the singlet of methacrylate methyl group at $\delta = 1.95$ into the doublet at $\delta = 1.17$ ppm as shown in Fig. 2.

Integration of the ^{1}H NMR signals enables quantitative characterisation of the course of the reactions. Thus, since disproportionation of HEMA yields EG and EGDMA in an equimolar ratio, conversion for this process (α_{disp}) can be

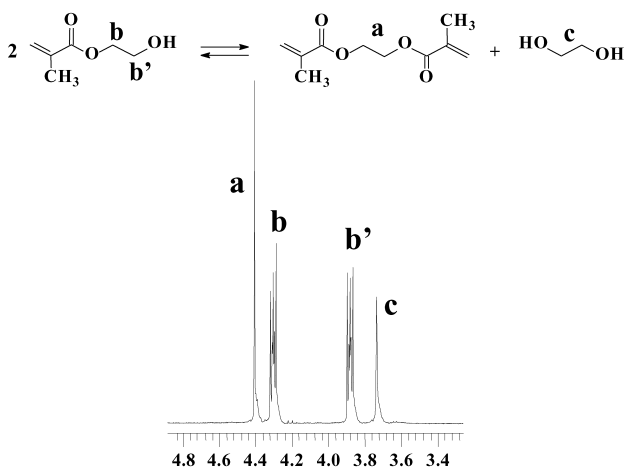


Fig. 1. Portion of ^{1}H NMR spectrum of HEMA disproportionation reaction mixture.

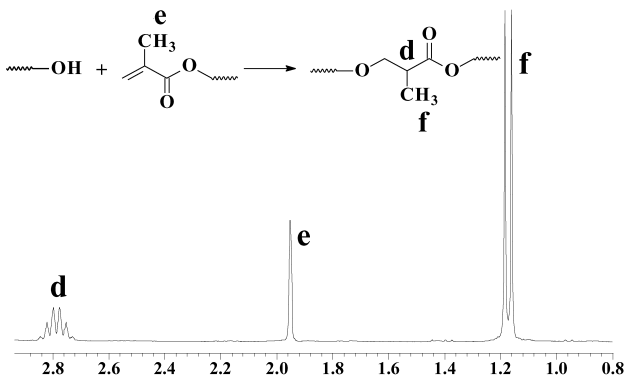


Fig. 2. Fragment of ^{1}H NMR spectrum presenting formation an oligomer via Michael-type addition.

expressed as:

$$\alpha_{disp} = \frac{I_a}{2I_0} \tag{1}$$

where I denotes intensities of the ^{1}H NMR signals;

$$I_0 = \frac{I_e + I_f}{3}.$$

Total conversion of HEMA (α_{tot}), i.e. in both the disproportionation (α_{disp}) and Michael addition (α_{add}) reactions should correspond to:

$$\alpha_{tot} = 1 - \frac{(I_b + I_{b'})}{4I_0} \tag{2}$$

On the other hand, if any other reaction did not proceed in the system, total conversion is:

$$\alpha_{tot} = \alpha_{disp} + \alpha_{add} \tag{3}$$

The intensities of the signals of the methyl groups enable calculation of the fraction of the C=C double bonds which underwent Michael addition (F_{add}) :

$$F_{add} = \frac{I_f}{I_e + I_f} \tag{4}$$

Finally, the values of conversion may be related to the

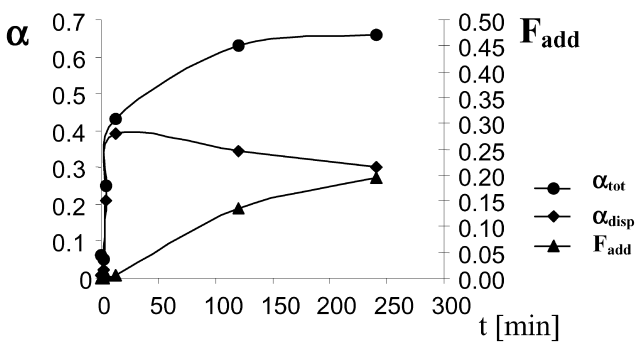


Fig. 3. ^{1}H NMR based quantitative data on conversion of HEMA in the presence of K_2CO_3 at 120 °C.

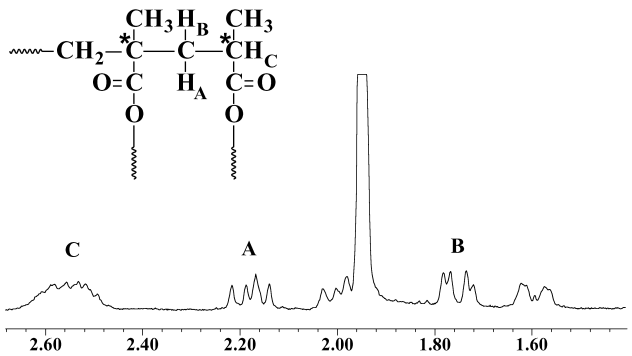


Fig. 4. Portion of ^{1}H NMR spectrum of a hydroxymethacrylate disproportionation/oligomerisation reaction mixture recorded after prolonged heating period.

number average degree of oligomerisation (m in Scheme 2):

$$\alpha_{add} = \alpha_{tot} - \alpha_{disp} = F_{add}\left(\frac{m}{m-1}\right) \quad (5)$$

A typical conversion/time relationship for HEMA-K_2CO_3 system is shown in Fig. 3. The disproportionation ⇆ transesterification reaches equilibrium in few minutes, the subsequent drop in value of α_{disp} is due to the consumption of EG and EGDMA via Michael addition. Since all the hydroxyl containing species can react with any methacrylate group in the system, the oligo(ether–ester) chain formed has irregular structure as it is indicated in Scheme 2.

The ^{1}H NMR based results are collected in Table 1. The 'optimal' temperature is that one at which the conversion of double bonds via Michael-type addition reached the highest value after 2 h, as it was determined individually for each the catalyst. At lower temperatures both the conversion and rate of the reaction decreased. At higher temperatures F_{add} values decreased as well, which is probably due to the Michael retro-addition reaction [12]. This was observed especially in the case of two the most active catalysts, appearing also to be the most efficient initiators, i.e. *t*-BuOK and NaH.

The best and the only way to obtain oligo(ether–ester)s of considerable molecular weight was to keep the reaction mixture 2 h at the 'optimal' temperature and then to leave for few days at room temperature. Without such a thermal pre-treatment oligomerisation did not proceed at all. When heating was continued beyond the period of 2 h, the mixture first became turbid and then gelled.

In our opinion, gelation is caused by competitive chain polymerisation of C=C bonds at this stage, either via anionic or free radical mechanism. Since some dimethacrylates had been always present in the reaction mixture (EGDMA, dimeric product of addition of HEMA to EGDMA and some dimethacrylate-like higher oligomers), formation of a network was inevitable.

The initial stage of the chain polymerisation of C=C bonds to yield carbon homochain has been observed in the ^{1}H NMR spectra of the reaction mixtures immediately before the gelation. Additional signals appear in the form of a pair of double doublets at $\delta = 2.18$ and $\delta = 1.76$ ppm (Fig. 4). They can be assigned to the unequivalent methylene protons in an aliphatic vicinity, both coupled additionally with the methine proton. The latter gives a broadened multiplet centered at $\delta = 2.55$ ppm. The coupling constants are of typical values and amount to: $J_{AB} = 14.0$ Hz, $J_{AC} = 8.5$ Hz and $J_{BC} = 4.5$ Hz. The second pair of double doublets at $\delta = 2.00$ and $\delta = 1.60$ ppm might correspond to an analogous system having a different configurational arrangement of neighbouring chiral carbons.

The other catalysing/initiating species from among basic or nucleophilic ones are much less (K_2CO_3, DBU) or quite not active (KOH) in Michael addition. Triphenylphosphine appeared to be inactive as well. Acidic species (*p*-TsOH, H_2SO_4) caused cleavage of oligooxyethylene chains in higher hydroxymethacrylates and the resulted mixtures were extremely complex. Therefore, we have selected NaH and *t*-BuOK to be used in subsequent experiments.

3.2. Preparation and characterisation of oligo(ether–ester)s

Oligomerisation of monomethacrylates of oligoethylene glycols, when performed according to the procedure established to be an optimal one, yielded crude reaction mixtures having ^{1}H NMR based final values of F_{add} in the

Table 2
Quantitative data on oligomers of OEGMMA

	oligo(HEMA)	oligo(DEGMMA)	oligo(TEGMMA)	oligo(TTEGMMA)
t-BuOK				
F_{add}	0.73	0.60	0.58	0.76
M_n (^{1}H NMR) (g/mol)	478	437	521	1 099
M_n (GPC) (g/mol)	723	693	738	731
MWD (GPC)	1.43	1.41	1.39	1.55
NaH				
F_{add}	0.71	0.73	0.70	0.73
M_n (^{1}H NMR) (g/mol)	609	639	723	991
M_n (GPC) (g/mol)	736	932	1 149	952
MWD (GPC)	1.53	1.44	1.51	1.44

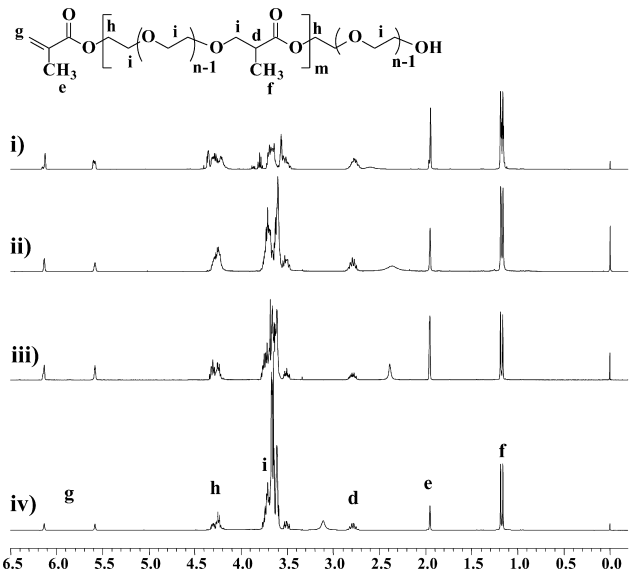


Fig. 5. ^{1}H NMR spectra of oligo(ether–ester)s of HEMA (i), DEGMMA (ii), TEGMMA (iii), TTEGMMA (iv).

range of 0.41–0.57. After washing off unreacted monomers and other low molecular weight species F_{add} increased to 0.60–0.76, as quoted in Table 2. The oligomers were characterised by use of ^{1}H NMR, GPC and ESI-MS. An

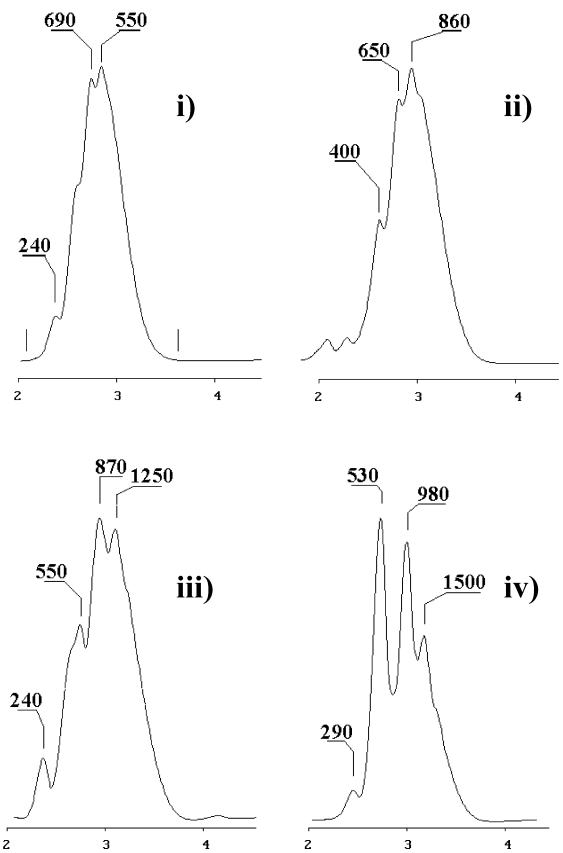


Fig. 6. GPC traces of oligo(ether–ester)s of HEMA (i), DEGMMA (ii), TEGMMA (iii), TTEGMMA (iv).

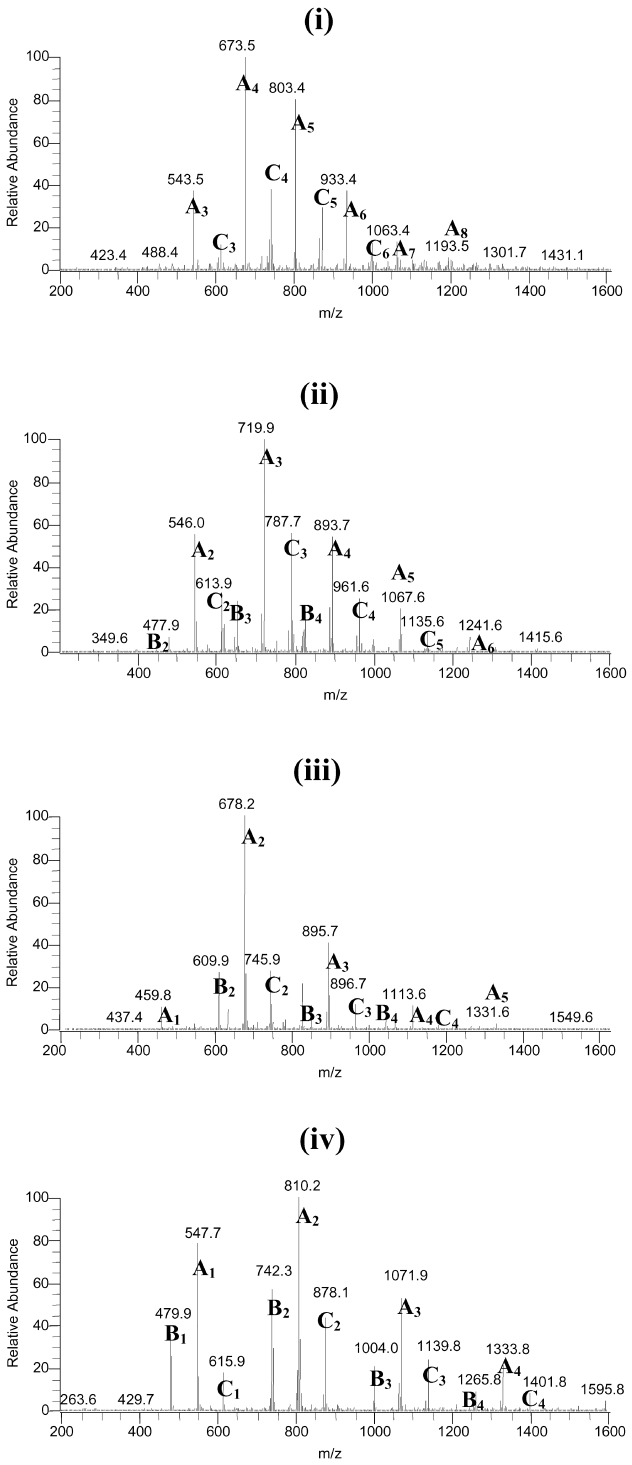
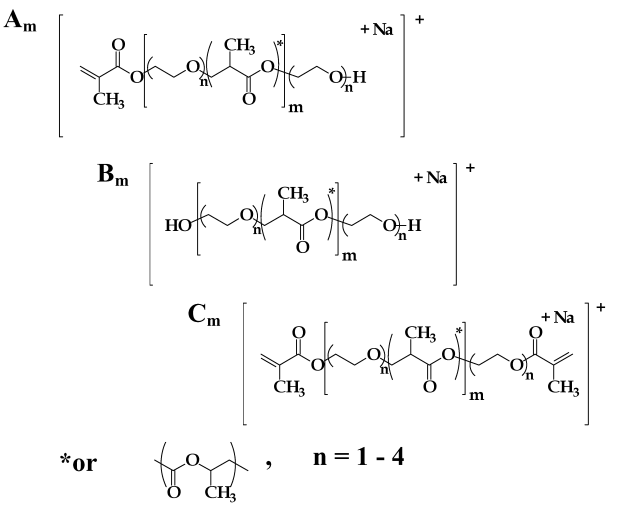


Fig. 7. ESI-MS spectra of oligo(ether–ester)s of HEMA (i), DEGMMA (ii), TEGMMA (iii), TTEGMMA (iv).

interesting feature of oligo(TTEGMMA) has been revealed, i.e. water solubility and lower critical solution temperature (LCST) behavior at ca. 42.5 °C, which is to be investigated in detail in future [13].

A set of ^{1}H NMR spectra of particular oligo(OEGMMA)s is presented in Fig. 5. Values of F_{add} enabled



Scheme 3.

calculation of number average molecular weights collected in Table 2.

The latter are more or less consistent with those based on GPC measurements (Fig. 6, Table 2).

Molecular weight distribution values are rather narrow ranging from 1.29 to 1.51 (3–6 in the crude reaction mixtures).

Both the molecular weight range and detailed structure of oligo(OEGMMA)s have been examined by ESI-MS technique (Fig. 7). The molecular ion *m*/*z* values prove existence of three possible oligo(ether–ester) structures having different set of end groups, as shown in Scheme 3. Formation of cyclic structures via intramolecular Michael addition can be considered as well, especially based on TTEGMMA and/or oligomers of the type A. However, till now there is no experimental evidence for that based on the results obtained.

Dihydroxy terminated oligomers of HEMA have not been detected, unlike for the hydroxymethacrylates having $n = 2–4$. In general, oligomers having m in the range of up to 8 have been detected by the technique while the most abundant ions usually corresponded to $m = 3–5$. Fragmentation mechanism for particular species has been investigated as well and the results are to be published in a separate paper [14].

4. Conclusions

Monomethacrylates of oligoethylene glycols, though being known to be hardly accessible to Michael-type addition, can be polymerised via this mechanism to yield oligo(ether–ester)s having molecular weight in order of one thousand. The best way to do that was to heat the monomer 2 h at 100 or 80 °C in the presence of *t*-BuOK or NaH, respectively, and next to leave the reaction mixture to stand for few days at room temperature. The oligomerisation proceeds slowly by step-growth addition mechanism accompanying fast, equilibrium disproportionation of the initial monomers to corresponding glycols and dimethacrylates. Since the latter can take part in the oligomerisation as well, the resulting oligo(ether–ester)s have an irregular structure. Nevertheless, due to the presence of terminal primary hydroxyl groups and methacrylate double bonds, the oligomers of the type A (Scheme 3) can be considered as macromonomers of potential use, e.g. biomedical one, especially that ether–ester chain may be degraded in both a basic and an acidic environment.

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