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Brotherton, E.E., Jesson, C.P., Warren, N.J. et al. (2021) New aldehyde-functional methacrylic water-soluble polymers. *Angewandte Chemie International Edition*, 60 (21). pp. 12032-12037. ISSN: 1433-7851

<https://doi.org/10.1002/anie.202015298>

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Water-Soluble Polymers

New Aldehyde-Functional Methacrylic Water-Soluble Polymers

Emma E. Brotherton, Craig P. Jesson, Nicholas J. Warren, Mark J. Smallridge, and Steven P. Armes*

Abstract: Aldehyde groups enable facile conjugation to proteins, enzymes, oligonucleotides or fluorescent dyes, yet there are no literature examples of water-soluble aldehyde-functional vinyl monomers. We report the synthesis of a new hydrophilic *cis*-diol-based methacrylic monomer (GEO5MA) by transesterification of isopropylidenglycerol penta(ethylene glycol) using methyl methacrylate followed by acetone deprotection via acid hydrolysis. The corresponding water-soluble aldehyde monomer, AGEOSMA, is prepared by aqueous periodate oxidation of GEO5MA at 22 °C. RAFT polymerization of GEO5MA yields the water-soluble homopolymer, PGEO5MA. Aqueous periodate oxidation of the terminal *cis*-diol units on PGEO5MA at 22 °C affords a water-soluble aldehyde-functional homopolymer (PAGEOSMA). Moreover, a library of hydrophilic statistical copolymers bearing *cis*-diol and aldehyde groups was prepared using sub-stoichiometric periodate/*cis*-diol molar ratios. The aldehyde groups on PAGEOSMA homopolymer were reacted in turn with three amino acids to demonstrate synthetic utility.

Introduction

Aldehydes are extremely useful functional groups in synthetic organic chemistry: they can be oxidized to give carboxylic acids, reduced to afford alcohols, undergo Schiff base chemistry and also form (hemi)acetals.^[1] In the field of synthetic polymer chemistry, aldehyde-based initiators^[2–8] have been utilized to prepare various types of aldehyde-functional polymers. Alternatively, Bilgic and Klok derivatized poly(2-hydroxyethyl methacrylate) brushes under oxidative conditions in order to introduce aldehyde groups for subsequent oligonucleotide conjugation.^[9] However, surprisingly few aldehyde-functional monomers have been reported in the literature.^[10,11,12–25] Most of these examples are hydro-

phobic (e.g. 4-vinylbenzaldehyde) and hence produce water-insoluble polymers.^[16,19–23,26–32] This is unfortunate, because aldehyde groups enable facile conjugation to peptides/proteins and water-soluble dyes in aqueous solution under mild conditions.^[2–5,10,25,33–38] In principle, this problem can be circumvented by statistical copolymerization of the hydrophobic aldehyde-functional monomer with a sufficiently hydrophilic comonomer.^[12,13,15,25,33,39] Alternatively, the incorporation of a terminal protected aldehyde moiety onto a poly(ethylene glycol) (PEG) chain has been utilized to confer aldehyde functionality under aqueous conditions.^[5–8,40,41] Nevertheless, despite the remarkable progress made in synthetic polymer chemistry over the past few decades, there seem to be few, if any, literature examples of hydrophilic aldehyde-functional vinyl monomers and their corresponding water-soluble homopolymers.

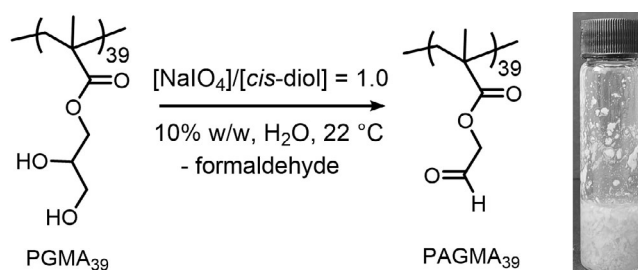
One well-known route to aldehyde-terminated water-soluble polymers is the selective oxidation of the minor fraction of *cis*-diol units within poly(vinyl alcohol).^[42] This water-soluble polymer can be obtained via hydrolysis of poly(vinyl acetate), which contains such *cis*-diols as defect sites resulting from a small amount of head-to-head coupling during the free radical homopolymerization of vinyl acetate.^[43] Oxidation is readily achieved in aqueous solution under mild conditions using sodium periodate to afford aldehyde-capped poly(vinyl alcohol) chains.^[44] Inspired by this well-established chemistry, we recently decided to investigate the periodate oxidation of poly(glycerol monomethacrylate) (PGMA) to produce an aldehyde-functional methacrylic polymer (Scheme 1; Supporting Information). However, periodate oxidation of a 10% w/w aqueous solution of PGMA₃₉ at 22 °C merely produced a macroscopic precipitate. This suggests that the target aldehyde-functional methacrylic homopolymer (PAGMA) is actually hydrophobic. In principle, such precipitation could be the result of reaction between

[*] E. E. Brotherton, Dr. C. P. Jesson, Dr. N. J. Warren, Prof. S. P. Armes
Chemistry, The University of Sheffield
Dainton Building, Brook Hill, Sheffield, S3 7HF (UK)
E-mail: s.p.arnes@sheffield.ac.uk

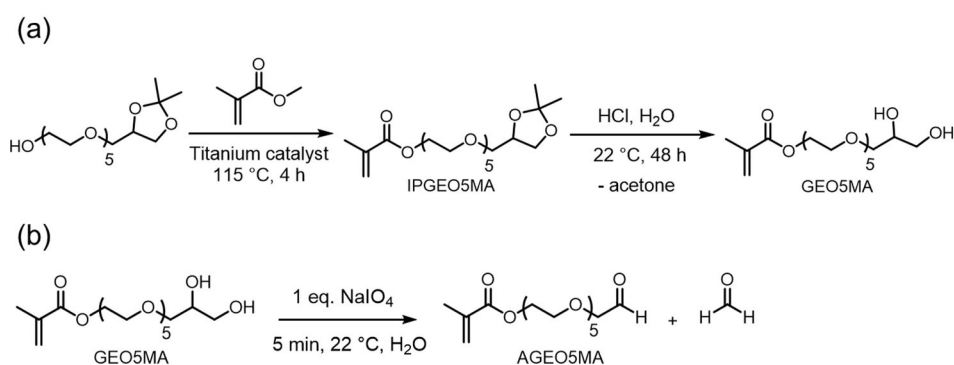
M. J. Smallridge
GEO Specialty Chemicals
Charleston Road, Hardley, Hythe, Southampton, SO45 3ZG (UK)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.202015298>.

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Scheme 1. Selective oxidation of a water-soluble PGMA₃₉ homopolymer precursor using a stoichiometric amount of sodium periodate in aqueous solution at 22 °C affords PAGMA₃₉ as a water-insoluble precipitate.



Scheme 2. a) Two-step synthesis of GEO5MA monomer starting from an isopropylidene glycerol precursor as a hydroxy-functional initiator. This precursor is then transesterified with methyl methacrylate to produce IPGEO5MA, before removing the ketal protecting group with acid to afford GEO5MA monomer. b) Oxidation of GEO5MA in aqueous solution using sodium periodate at 22 °C affords AGEO5MA with formaldehyde as a by-product. The same selective oxidation can be used to convert PGE05MA homopolymer into PAGE05MA homopolymer using identical reaction conditions.

the *cis*-diol and aldehyde units at intermediate conversion. However, reaction exotherms (data not shown) and visual inspection of the reaction mixtures suggest that the timescale required for the *cis*-diol oxidation is much shorter than that for precipitation. Thus, it seems more likely that intermolecular crosslinking occurs between geminal diols and aldehydes (Supporting Information, Scheme S1).

In view of these problems, we designed a new *cis*-diol-based methacrylic monomer (GEO5MA; Scheme 2a). We envisaged that the pendent oligo(ethylene glycol) moiety in GEO5MA should confer sufficient hydrophilic character to ensure water solubility after converting its terminal *cis*-diol group into an aldehyde via periodate oxidation to form either AGE05MA monomer (Scheme 2b) or the corresponding PAGE05MA homopolymer.

Results and Discussion

The two-step synthesis of GEO5MA monomer was conducted on a 1.2 kg scale via 1) transesterification of isopropylidene glycerol penta(ethylene glycol) using methyl methacrylate to afford IPGEO5MA (Scheme 2a) and 2) acid hydrolysis to remove the acetone protecting group (Supporting Information). The chemical structure of this new methacrylic monomer was confirmed by ^1H and ^{13}C NMR spectroscopy (Figure 1a; Supporting Information, Figure S1a), mass spectrometry, elemental microanalysis and FT-IR spectroscopy (Supporting Information). The integrated signals in the ^1H NMR spectrum are consistent with the proposed monomer structure. Its ^{13}C NMR spectrum contained ten distinct signals. A characteristic signal at ≈ 160 ppm was assigned to the ester carbonyl carbon; its relatively low intensity is attributed to the slow relaxation time for such quaternary carbon atoms.^[45] The presence of a methacrylate group is confirmed by signals at 135 and 127 ppm. Several signals between 62.6 and 71.3 ppm are assigned to the pendent oligo(ethylene glycol) chain and include characteristic signals for the carbons attached to hydroxyl groups. According to mass spectrometry, the number of ethylene

glycol units per oligo(ethylene glycol) group ranged from 2 to 7, with a mean value of 5.

Oxidation of a 10% w/w aqueous solution of GEO5MA using a NaIO_4 /*cis*-diol molar ratio of unity (Scheme 2b) led to essentially complete oxidation of the terminal *cis*-diol units within 5 min at 22 °C, as confirmed by ^1H NMR spectroscopy (Figure 1). The structure of this new AGE05MA monomer was confirmed by mass spectrometry, elemental microanalysis, ^1H and ^{13}C NMR (Figure 1b; Figure S1b) and FT-IR spectroscopy (Figure S3a). Two new signals ap-

pear at 9.52 and 5.09 ppm in the ^1H NMR spectrum for AGE05MA, corresponding to an aldehyde group and a geminal diol, respectively. The aldehyde/geminal diol molar ratio was 0.034, which indicates that AGE05MA exists primarily in its hydrated geminal diol form in D_2O (Figure 1b). Similar observations have been reported for other hydrophilic aldehydes in aqueous solution, such as acetaldehyde (Figure S2).^[46–49] During the periodate oxidation of GEO5MA to form AGE05MA, the starting material can in principle react with the product to generate dimethacrylate species via (hemi)acetal chemistry.^[1] In practice, the final product contains less than 1% dimethacrylate impurity as estimated by ^1H NMR spectroscopy. The ^{13}C NMR spectrum also shows the appearance of two new signals at 169.5 and 88.0 ppm, which correspond to the aldehyde carbon and the geminal diol carbon, respectively. After purification by extraction with CH_2Cl_2 , the RAFT aqueous solution polymerization of AGE05MA was conducted using a dicarboxylic acid-functionalized water-soluble RAFT agent (CECPA) to

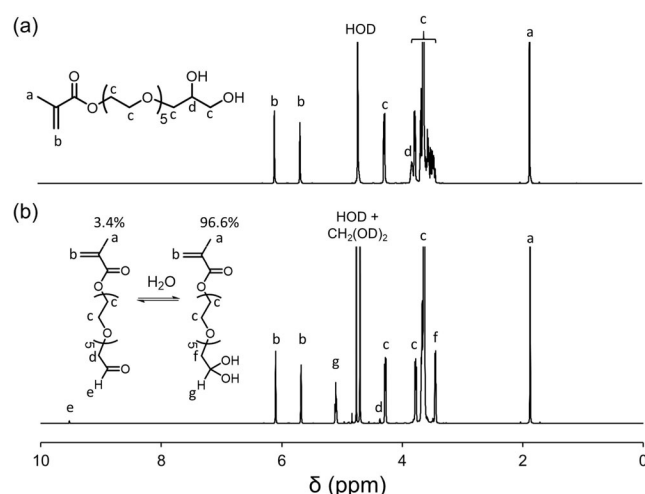


Figure 1. ^1H NMR spectra (D_2O) recorded for a) GEO5MA monomer and b) AGE05MA monomer ($\text{CH}_2(\text{OD})_2$ denotes the hydrated form of formaldehyde).

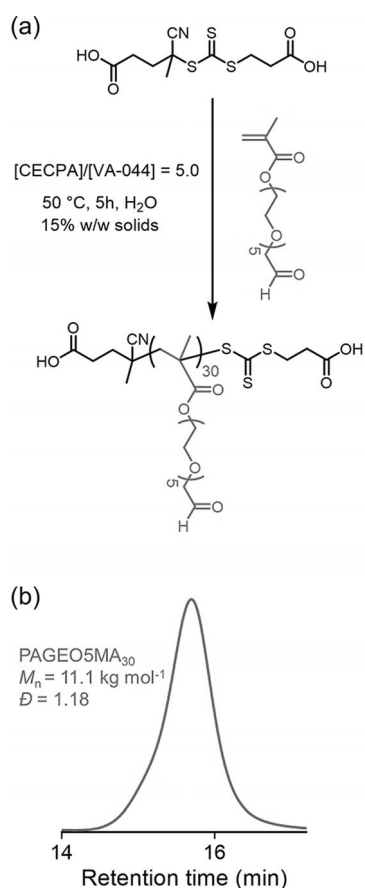


Figure 2. a) Synthesis of PAGEO5MA₃₀ via RAFT aqueous solution polymerization of AGEO5MA using a water-soluble dicarboxylic acid-functionalized RAFT agent (CECPA). b) DMF GPC trace for the resulting PAGEO5MA₃₀ homopolymer (molecular weight data expressed relative to poly(methyl methacrylate) calibration standards).

target a mean degree of polymerization (DP) of 30 (Figure 2a). More than 99% conversion was achieved and the resulting PAGEO5MA₃₀ was well-defined, as indicated by its relatively narrow, unimodal GPC trace ($M_n = 11\ 100\ \text{g mol}^{-1}$; $D = 1.18$; Figure 2b). ¹H NMR signals for the terminal aldehyde and geminal diol groups were detected for this homopolymer (aldehyde/geminal diol molar ratio = 0.041).

Alternatively, RAFT aqueous solution polymerization of GEO5MA affords a near-monodisperse PGEO5MA₃₇ homopolymer ($M_n = 17\ 200\ \text{g mol}^{-1}$; $D = 1.18$). When a NaIO₄/*cis*-diol molar ratio of unity was used to derivatize this precursor, essentially complete oxidation was achieved to afford PAGEO5MA₃₇ homopolymer within 5 min at 22 °C (Table 1, Figure 3). The latter product proved to be water-soluble at concentrations of up to 15% w/w. In striking contrast, the product of the oxidation of PGMA₃₉ homopolymer using a stoichiometric amount of periodate, denoted hereafter as PAGMA₃₉, proved to be water-insoluble when prepared at 1.5 to 10% w/w (Supporting Information, Table S1). The much higher aqueous solubility observed for PAGEO5MA₃₇ is attributed to the hydrophilic oligo(ethylene glycol) units on each repeat unit.

Table 1: Extent of oxidation, DMF GPC molecular weight and dispersity data for the selective oxidation of PGEO5MA₃₇ in aqueous solution at 22 °C using (sub-)stoichiometric NaIO₄/*cis*-diol molar ratios ranging between 0 and 1.0.

NaIO ₄ / <i>cis</i> -diol molar ratio	Extent of oxidation [%]	M_n [kg mol ⁻¹]	D
1.00	> 99	16.5	1.22
0.75	78	15.9	1.24
0.50	49	16.8	1.21
0.10	11	17.4	1.22
0.00	0	17.2	1.18

However, only a minor fraction of monomer repeat units may need to be converted into aldehyde groups for certain applications. Thus, partial oxidation of a PGEO5MA₃₇ precursor using sub-stoichiometric quantities of NaIO₄ oxidant relative to its *cis*-diol groups was also investigated (schematic in Figure 3a).

Accordingly, utilizing NaIO₄/*cis*-diol molar ratios of 0.10, 0.50 or 0.75 produced a series of water-soluble P(GEO5MA_{*n*}-*stat*-AGEO5MA_{*m*})₃₇ statistical copolymers with approximate degrees of aldehyde functionality of 0.11, 0.49 and 0.78 respectively, as estimated from ¹H NMR spectroscopy studies (Table 1, Figure 3). Thus, the target degree of aldehyde functionality is always achieved (within experimental error). DMF GPC analyses confirmed that neither partial nor full oxidation of the PGEO5MA₃₇ homopolymer had a significant effect on its molecular weight distribution (Table 1; Figure S4). Moreover, using a slight excess of NaIO₄ relative to the pendent *cis*-diol groups also resulted in partial loss of the dithiobenzoate end-groups. Similarly, a PGEO5MA homopolymer ($M_n = 124.1\ \text{kg mol}^{-1}$, $D = 4.55$) was synthesized via free-radical polymerization in aqueous solution at 70 °C for 18 h. Selective oxidation of the *cis*-diol groups on this homopolymer also had minimal effect on its (broad) molecular weight distribution (Figures S5 and S6).

To investigate the scope of such new water-soluble aldehyde-functional polymers for conjugation with biologically-relevant compounds, PAGEO5MA₃₇ homopolymer was reacted in turn with three amino acids (glycine, lysine or cysteine; amino acid/aldehyde molar ratio = 1.0) to form the corresponding Schiff base, followed by in situ reductive amination using excess NaCNBH₃ (Scheme 3). These aqueous reaction mixtures were stirred at 35 °C for 48 h, with ¹H NMR spectroscopy studies indicating very high extents of reaction (> 99%) in each case (Figure S7). Aqueous GPC analysis of the resulting water-soluble polymers indicated that molecular weight distributions remained relatively narrow after this two-step one-pot derivatization (Figure S8).

This protocol was then extended to water-soluble diblock copolymers. A series of neutral, zwitterionic, cationic or anionic double-hydrophilic diblock copolymers was prepared in which one of the blocks was PGEO5MA (Scheme 4). For the neutral diblock copolymer, a trithiocarbonate-capped PEG₁₁₃ precursor was simply chain-extended via RAFT aqueous solution polymerization of GEO5MA at 50 °C. For the synthesis of the ionic diblock copolymers, a PGEO5MA₃₇ precursor was chain-extended via RAFT aqueous solution polymerization of 2-(methacryloyloxy)ethyl phosphoryl-

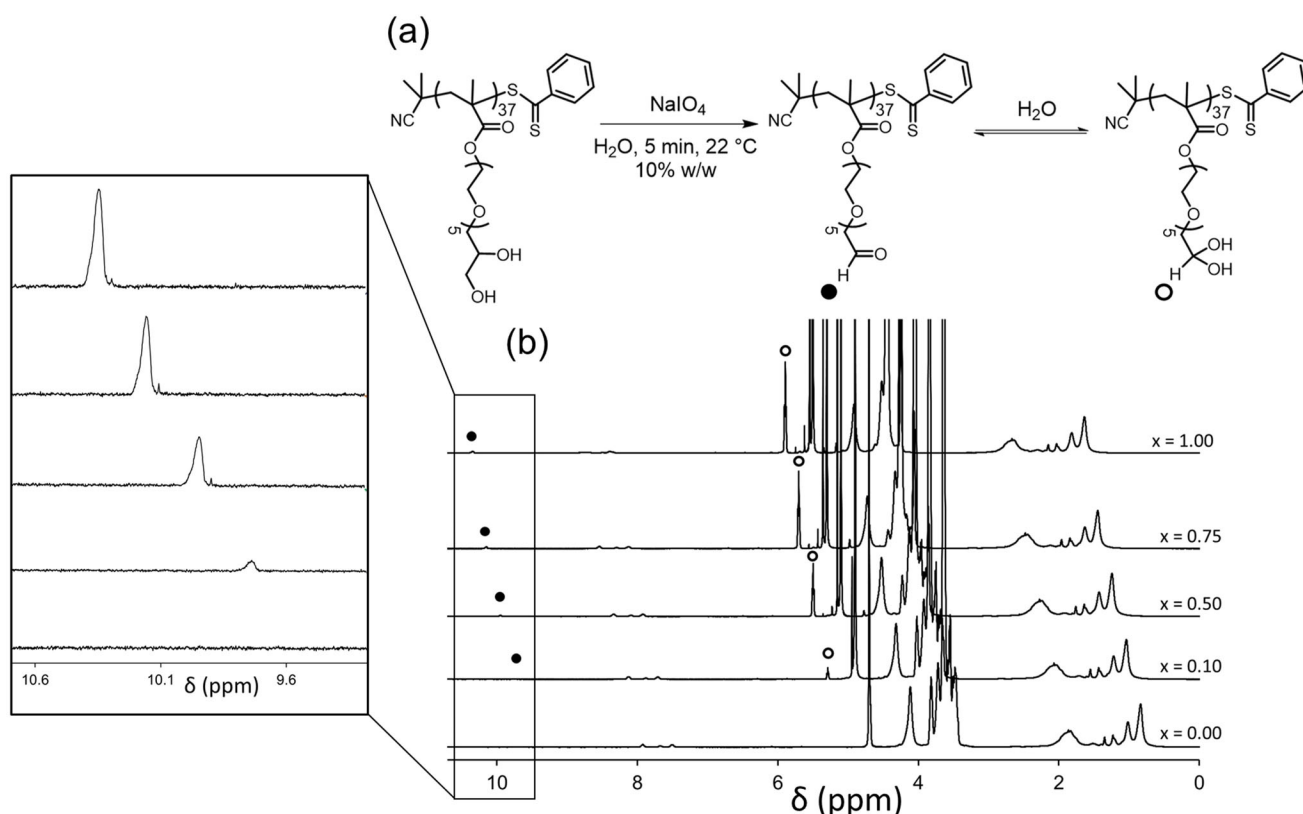
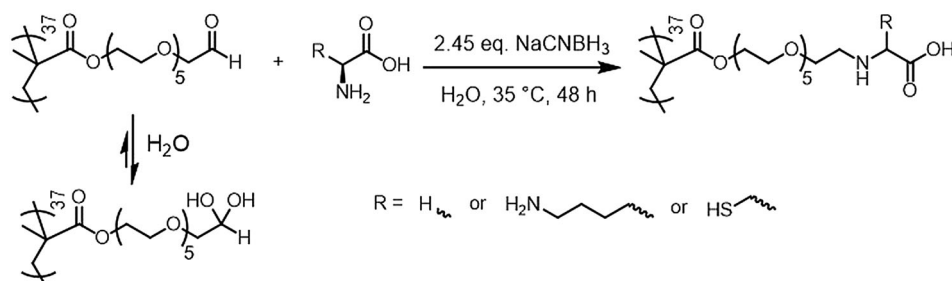


Figure 3. a) Reaction scheme for the (partial) oxidation of a near-monodisperse PGEO5MA₃₇ precursor in aqueous solution using NaIO₄ at 22 °C. Adjusting the NaIO₄/*cis*-diol molar ratio (*x*) between 0.1 and 1.0 generates a library of aldehyde-functional water-soluble statistical copolymers. b) Offset ¹H NMR spectra (D₂O) recorded for PGEO5MA₃₇, P(GEO5MA_{*m*}-stat-AGEO5MA_{*m*})₃₇ (where *m* = 0.11, 0.49 and 0.78), and PAGEO5MA₃₇.

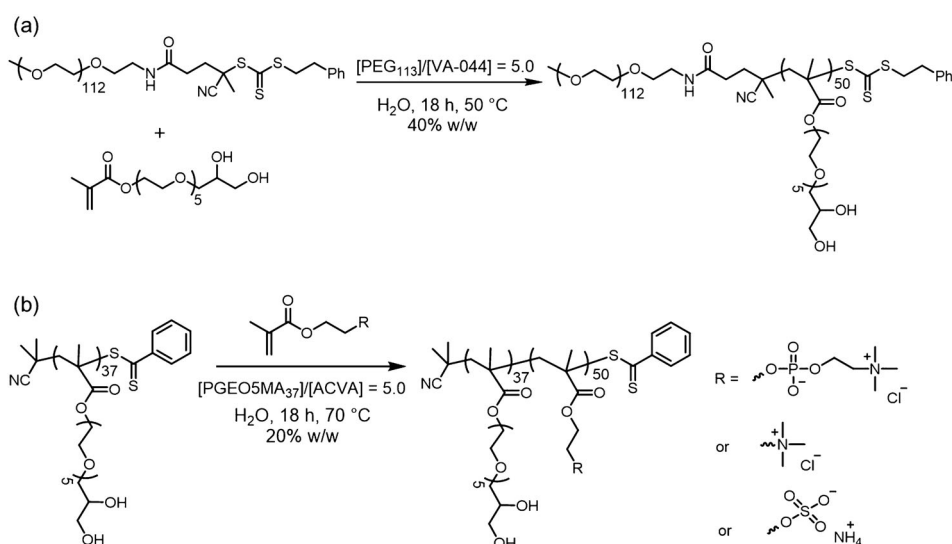


Scheme 3. Schiff base reaction of PAGEO5MA₃₇ with an amino acid (e.g., glycine, lysine, or cysteine) followed by reductive amination using excess aqueous NaCNBH₃ at 35 °C to afford a series of new zwitterionic homopolymers via a two-step one-pot wholly aqueous protocol.

choline (MPC), [2-(methacryloyloxy)ethyl] trimethylammonium chloride (METAC) or ammonium 2-sulfatoethyl methacrylate (SEM) at 70 °C. Each polymerization was allowed to proceed overnight to ensure high monomer conversion ($\geq 98\%$ in all cases, as confirmed by ¹H NMR spectroscopy; Table 2).

DMF GPC analysis indicated a high blocking efficiency for the RAFT solution polymerization of GEO5MA using the PEG₁₁₃ macro-CTA and the resulting PEG₁₁₃-PGEO5MA₅₀ diblock copolymer had a relatively low dispersity ($\mathcal{D} = 1.20$; Table 2; Figure S9a). However, aqueous GPC analysis was required to assess the molecular weight distributions of the ionic diblock copolymers. (Table 2; Figures S9b–d). Oxida-

tion of the pendent *cis*-diol groups on the PGEO5MA_{*x*} chains was investigated using a NaIO₄/*cis*-diol molar ratio of unity at a diblock copolymer concentration of 20 % w/w. According to ¹H NMR analysis, the extent of derivatization was at least 99 % in all cases (Table 2). DMF GPC analysis confirmed that periodate oxidation had minimal effect on the molecular weight distribution ($\mathcal{D} = 1.22$; Figure S9a) in the case of the PEG₁₁₃-PGEO5MA₅₀ diblock copolymer. Similar results were obtained for the zwitterionic, cationic and anionic diblock copolymers when using aqueous GPC (Table 2; Figures S9b–d).



Scheme 4. a) Reaction scheme for the synthesis of PEG₁₁₃-PGE05MA₅₀ via RAFT aqueous solution polymerization of GEO5MA at 40% w/w solids using a PEG₁₁₃/VA-044 molar ratio of 5.0 at 50 °C. b) Reaction scheme for the synthesis of PGE05MA₃₇-PX₅₀ diblock copolymers (where X = MPC, METAC or SEM) at 20% w/w solids using a PGE05MA₃₇/ACVA molar ratio of 5.0.

Table 2: Summary of monomer conversions, extents of *cis*-diol oxidation and GPC molecular weight data for a series of neutral, zwitterionic, cationic and anionic diblock copolymers (with reference homopolymers included for comparison).

GPC eluent	Polymer composition	Monomer conversion [%]	Extent of <i>cis</i> -diol oxidation [%]	M_n [kg mol ⁻¹] ^[c]	\mathcal{D}
DMF	PEG ₁₁₃	–	–	5.0	1.13
DMF	PEG ₁₁₃ -PGE05MA ₃₇	> 99	–	27.7	1.20
DMF	PEG ₁₁₃ -PAGE05MA ₃₇	–	> 99	26.2	1.22
Aqueous ^[a]	PGE05MA ₃₇	–	–	5.8	1.29
Aqueous ^[a]	PGE05MA ₃₇ -PMPC ₅₀	> 99	–	13.1	1.34
Aqueous ^[a]	PAGE05MA ₃₇ -PMPC ₅₀	–	99	13.4	1.38
Aqueous ^[b]	PGE05MA ₃₇	–	–	–	–
Aqueous ^[b]	PGE05MA ₃₇ -PMETAC ₅₀	98	–	23.4	1.12
Aqueous ^[b]	PAGE05MA ₃₇ -PMETAC ₅₀	–	> 99	23.3	1.11
Aqueous ^[a]	PGE05MA ₃₇	–	–	5.7	1.34
Aqueous ^[a]	PGE05MA ₃₇ -PSEM ₅₀	> 99	–	11.0	1.30
Aqueous ^[a]	PAGE05MA ₃₇ -PSEM ₅₀	–	> 99	12.7	1.36

[a] 0.2 M NaIO₃, 0.05 M TRISMA buffer, pH 7. [b] 0.5 M acetic acid, 0.3 M NaH₂PO₄, pH 2. [c] Relative to PEG/PEO standards.

Conclusion

In summary, we have reported the atom-efficient synthesis of a new *cis*-diol-based methacrylic monomer (GEO5MA) that is readily converted into a hydrophilic aldehyde-functional monomer (AGE05MA) via selective oxidation using NaIO₄ in aqueous solution. Unlike almost all other literature examples of aldehyde-based vinyl monomers, this latter monomer is water-soluble and can be polymerized with good control via RAFT aqueous solution polymerization. Alternatively, homopolymerization of the GEO5MA precursor under similar conditions affords a well-defined water-soluble PGE05MA precursor that can be converted into PAGE05MA under mild conditions using a stoichiometric amount of NaIO₄ oxidant. On the other hand, using sub-stoichiometric quantities of NaIO₄ relative to the pendent *cis*-diol units

produces a range of water-soluble aldehyde-functional statistical copolymers. New PAGE05MA-based double-hydrophilic diblock copolymers can be prepared and model Schiff base reactions have been conducted in aqueous solution under mild conditions using various amino acids to introduce zwitterionic groups. We anticipate that this new hydrophilic aldehydic vinyl monomer and its corresponding copolymers will offer a range of potential applications in the fields of cell biology and biomaterials.

Acknowledgements

We thank EPSRC and GEO Specialty Chemicals for funding CDT PhD studentships for E.E.B. and C.P.J. (EP/L016281). GEO Specialty Chemicals (Hythe, UK) is acknowledged for permission to publish this work. Dr. K.I.A. Doudin is thanked for his help with acquisition of ¹³C NMR spectra for both PGE05MA₃₇ and PAGE05MA₃₇.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehyde-functional methacrylic monomers · block copolymers · periodate oxidation · RAFT polymerization

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Manuscript received: November 16, 2020

Revised manuscript received: February 15, 2021






Accepted manuscript online: February 22, 2021

Version of record online: ■ ■ ■ ■ ■ ■ ■ ■ ■ ■

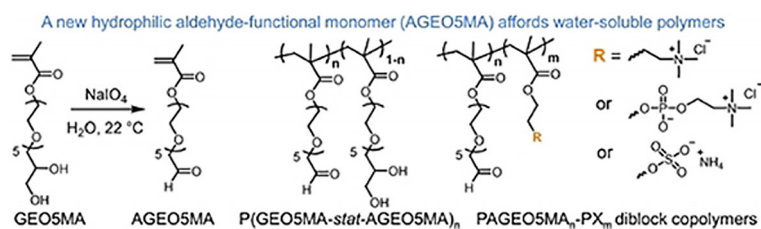
Research Articles



Water-Soluble Polymers

E. E. Brotherton, C. P. Jesson,
N. J. Warren, M. J. Smallridge,
S. P. Armes*     

New Aldehyde-Functional Methacrylic
Water-Soluble Polymers



A water-soluble aldehyde monomer (AGEO5MA) was prepared by oxidation of GEO5MA at 22 °C. RAFT aqueous polymerization yielded PAGEO5MA homopolymer, which was oxidized using sub-stoichiometric periodate/*cis*-diol

molar ratios to yield hydrophilic statistical copolymers with *cis*-diol and aldehyde groups. Three PAGEO5MA-based diblock copolymers were converted into aldehyde-functional copolymers, which were derivatized with amino acids.

