Synthesis and aqueous solution properties of novel zwitterionic block copolymers

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A series of near-monodisperse poly[2-(dimethylamino)ethyl methacrylate-*block*-2-tetrahydropyranyl methacrylate] precursors is synthesised using group-transfer polymerisation chemistry; the 2-tetrahydropyranyl methacrylate protecting group is quantitatively removed under mild conditions and the resulting zwitterionic block copolymers undergo reversible temperature-induced micellisation in aqueous media.

Over the last decade or so group-transfer polymerisation[1,2] has become recognised as an excellent method for the synthesis of methacrylate (co)polymers of controlled structure and narrow molecular mass distribution. Recently we have used this technique to prepare well defined homopolymers and block copolymers based on 2-(dimethylamino)ethyl methacrylate (DMAEMA).[3,4] DMAEMA homopolymer is a weak polybase which is soluble at neutral pH or in acidic media due to protonation of the tertiary amine groups. Over the last few years we have explored several synthetic routes to zwitterionic DMAEMA-based block copolymers using *tert*-butyl methacrylate and benzyl methacrylate as protected monomers for methacrylic acid residues. GPC analysis of a DMAEMA homopolymer treated under conditions required for quantitative removal of the *tert*-butyl group in poly(*tert*-butyl methacrylate) [toluene-*p*-sulfonic acid, 80 °C for 7 h in toluene–methanol (5 : 1)] indicated some degree of intermolecular cross-linking between the DMAEMA residues, showing this protecting group to be unsuitable.[5] The alternative benzyl protecting group is normally readily removed by catalytic hydrogenolysis[6,7] but we found only minimal deprotection of DMAEMA–benzyl methacrylate block copolymers; this is believed to be due to catalyst poisoning by the tertiary amine groups. Prompted by a recent disclosure by Teyssie and coworkers[8] we now describe a facile route to well defined zwitterionic block copolymers using 2-tetrahydropyranyl methacrylate (THPMA) as the protected monomer.† This protecting group is easily removed by acid hydrolysis at room temp. to yield near-monodisperse zwitterionic DMAEMA–methacrylic acid block copolymers (Fig. 1). In contrast, we found that the deprotection route favoured by Patrickios *et al.*[9]‡ for DMAEMA–methyl methacrylate–THPMA triblocks was unsatisfactory: the appearance of a band at *ca.* 1806 cm^{-1} in the IR spectrum of the deprotected polymer indicated significant anhydride formation had occurred after thermolysis for 48 h at 140 °C. Furthermore, our control experiments with DMAEMA homopolymer suggested that intermolecular cross-linking of the DMAEMA residues occurs under these thermolysis conditions.[5]

A series of DMAEMA–THPMA block copolymers was prepared using group-transfer polymerisation under conditions similar to those previously described.[4] All copolymerisations were carried out using 1-methoxy-1-trimethylsiloxy-2-methylprop-1-ene (MTS) as initiator and tetrabutylammonium dibenzoate (TBADB) as catalyst at 25 °C in dry THF using Schlenk techniques. The DMAEMA monomer was polymerised first and near-quantitative copolymer yields were obtained in all syntheses. The relative proportions of the two comonomers were varied at a fixed monomer/initiator ratio in order to control the copolymer composition. Comonomer/initiator ratios were varied in order to control the copolymer molecular mass. The molecular masses, polydispersities and compositions of the resulting block copolymers are summarised in Table 1. Narrow molecular mass distributions were obtained in all cases ($M_w/M_n \leqslant 1.22$) as judged by gel permeation chromatography (THF eluent, PMMA standards, RI detector). The actual copolymer compositions as determined by ^{1}H NMR spectroscopy corresponded within experimental error to those expected from the comonomer feeds. The DMAEMA–THPMA copolymers were either dissolved or dispersed (depending on the DMAEMA content) in 0.1 M HCl at 25 °C. Complete

Table 1 A summary of the molecular masses, polydispersities, copolymer compositions and isoelectric points of the DMAEMA–THPMA block copolymers determined using gel permeation chromatography, ^{1}H NMR spectroscopy and acid titration, respectively

Sample	Observed M_n[a]	DMAEMA–THPMA copolymer composition[b]	M_w/M_n[a]	Observed isoelectric point[c]
AB1	8 500	77 : 23	1.08	—
AB2	24 700	82 : 18	1.16	8.56
AB3	35 700	64 : 36	1.15	7.40
AB4	34 000	51 : 49	1.22	6.74
AB5	42 400	43 : 57	1.19	5.62

[a] As determined by GPC (THF), calibrated with PMMA standards. [b] As determined by ^{1}H NMR spectroscopy. [c] As determined by acid titration.

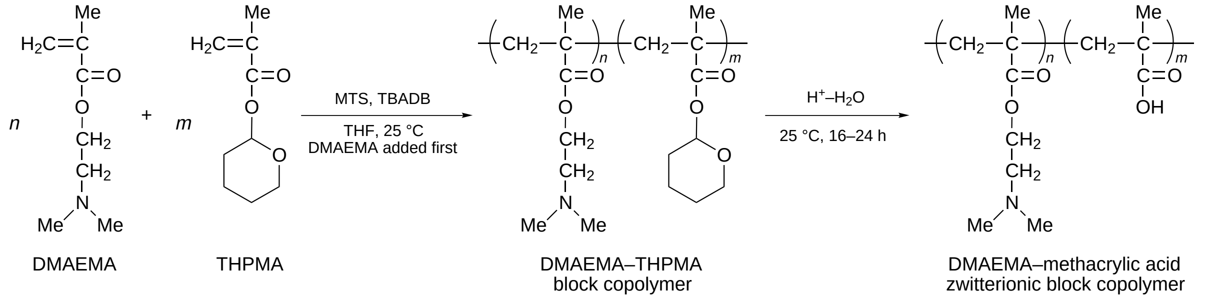

Fig. 1 Reaction scheme for the synthesis of the DMAEMA–methacrylic acid zwitterionic block copolymers *via* group-transfer polymerisation

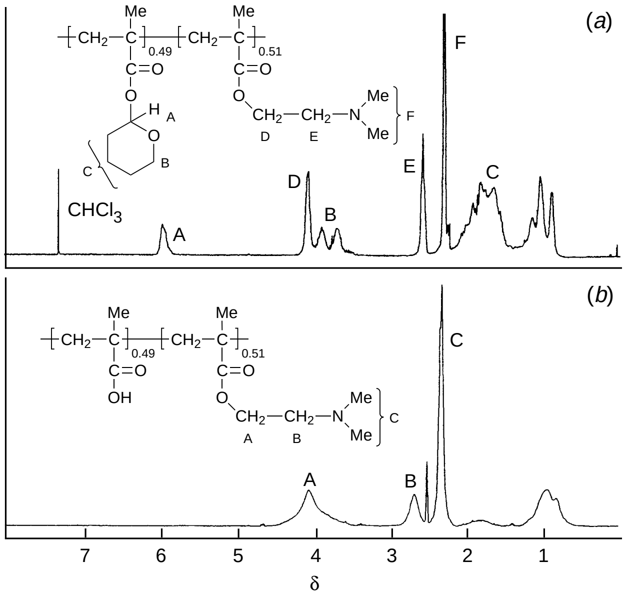

Fig. 2 Proton NMR spectra of (*a*) a 51 : 49 DMAEMA–THPMA block copolymer dissolved in $CDCl_3$; (*b*) the same block copolymer after acid hydrolysis under mild conditions dissolved in $(CD_3)_2SO$. Note the complete disappearance of the signals due to the THP group.

deprotection was achieved simply by stirring these aqueous solutions for 16–24 h at 25 °C.

Proton NMR spectra of a 51 : 49 DMAEMA–THPMA block copolymer before and after deprotection are shown in Fig. 2. The signals at δ 5.8–6.0 and 3.7–3.8 assigned to the THP protecting group disappear completely after acid hydrolysis. Despite the very mild deprotection conditions, it was considered prudent to verify that no side-reactions (*e.g.* chain scission or cross-linking) had occurred. This was confirmed by analysing the deprotected DMAEMA–methacrylic acid block copolymers using aqueous gel permeation chromatography (Pharmacia Superdex column; RI detector; PEG/PEO standards; TRIZMA pH 8.5 buffer in 1.0 M NaCl eluent at a flow rate of 1.5 ml min^{-1}). In all cases narrow, unimodal molecular mass distributions were obtained, with polydispersities comparable to those of the protected precursor blocks (M_w/M_n 1.18–1.24).

The isoelectric points (i.e.p.s) for the DMAEMA–methacrylic acid block copolymers were determined by acid titration and are summarised in Table 1. As expected, the i.e.p.s vary with block copolymer composition, with higher i.e.p.s being obtained for the more DMAEMA-rich copolymers. Precipitation of the copolymers occurred at their respective i.e.p.s: above and below the i.e.p.s the zwitterionic copolymers were soluble in aqueous media.

Examination of a 1.0% m/v solution of the 43 : 57 DMAEMA–methacrylic acid block copolymer in 0.01 M NaCl at pH 9.5 by dynamic light scattering (Malvern 4700 instrument, 80 mW argon ion laser, 90° scattering angle) confirmed very weak light scattering and unimer sizes at 25 °C. Heating this aqueous solution to 50 °C produced much more intense light scattering and visual inspection confirmed that the solution was slightly turbid. CONTIN analysis indicated the formation of near-monodisperse micellar aggregates with an intensity average diameter of 376 nm (see Fig. 3). This aggregation was completely reversible: the copolymer solution became optically transparent again on cooling. In the absence of 0.01 M NaCl, micellar aggregates of *ca*. 700 nm were obtained. At pH 9.5 the methacrylic acid residues should be fully ionised, whereas the DMAEMA residues are almost completely deprotonated.[10] The cloud-point temperature for a 1.0% m/v aqueous solution of DMAEMA homopolymer is in the range 32–46 °C depending on its molecular mass.[11] Thus, at 50 °C the interior of the micellar aggregates most likely contains the now hydrophobic DMAEMA block, with the ionised methacrylic acid block forming the solvated micellar corona.

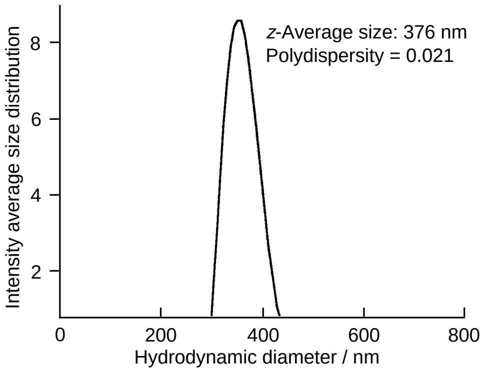

Fig. 3 Intensity average size distribution of the micellar aggregates formed at 50 °C in a 1.0% m/v aqueous solution of a 43 : 57 DMAEMA–methacrylic acid zwitterionic block copolymer in the presence of 0.01 M NaCl at pH 9.5

According to Teyssie and coworkers[8] and Patrickios *et al.*,[9] potential applications for these new zwitterionic copolymers include pigment dispersion and protein separation, respectively. The reversible micellisation behaviour observed in aqueous media also suggests potential drug delivery applications.

The EPSRC and ICI Paints are thanked for a CASE D.Phil. studentship for A. B. L. An EPSRC ROPA grant (GR/K86855) was used to purchase the argon-ion laser for the dynamic light scattering studies.

Footnotes

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† The 2-tetrahydropyranyl methacrylate monomer is not commercially available: it was synthesised by reacting methacrylic acid with 3,4-dihydro-2*H*-pyran at 55 °C using 50% sulfuric acid as catalyst. The crude monomer was dried and distilled under vacuum prior to passage through a basic alumina column to remove residual methacrylic acid.

‡ These workers also used trimethylsilyl methacrylate as a protecting group for triblock copolymers containing methacrylic acid residues. There are no deprotection problems associated with this monomer but it is well known that, under GTP conditions, its polymerisation is slow and incomplete (see ref. 7).

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Received in Bath, UK, 14th March 1997; Com. 7/02116J