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Polymer 42 (2001) 5993–6008

polymer

www.elsevier.nl/locate/polymer

Synthesis and aqueous solution properties of near-monodisperse tertiary amine methacrylate homopolymers and diblock copolymers

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Received 13 December 2000

Abstract

Group transfer polymerisation (GTP) of four tertiary amine methacrylates, 2-(dimethylamino)ethyl methacrylate (DMA), 2-(diethylamino)ethyl methacrylate (DEA), 2-(diisopropylamino)ethyl methacrylate (DPA) and 2-(*N*-morpholino)ethyl methacrylate (MEMA) produced a series of near-monodisperse homopolymers ($M_w/M_n < 1.15$). Molecular weights were controlled by varying the monomer/initiator ratio. The DMA and MEMA homopolymers were both water-soluble at 20°C in acidic or neutral media. Inverse temperature solubility behaviour was observed at higher temperatures, with cloud-points ranging from 32 to 53°C at pH 8. The Cloud-points decreased monotonically with increasing degrees of polymerisation, as expected. The MEMA homopolymers were particularly sensitive to the added electrolyte, with 'salting out' occurring at 20°C on addition of 0.2–0.3 M Na_2SO_4. The more hydrophobic DEA and DPA homopolymers were both insoluble at 20°C and neutral pH but readily dissolved as cationic polyelectrolytes in acidic media due to protonation of the tertiary amine residues. In addition, DMA was block copolymerized in turn with each of the other three tertiary amine methacrylate comonomers. These diblock copolymers could be dissolved molecularly without co-solvents in aqueous media at 20°C, with micellization occurring reversibly on judicious adjustment of the solution pH, temperature or electrolyte concentration. In all three cases, stable block copolymer micelles were formed with DMA coronas and hydrodynamic diameters of 20–60 nm. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Homopolymers; Copolymers; DMA

1. Introduction

Poly[2-(dimethylamino)ethyl methacrylate] is a weak polybase, which is water-soluble both at neutral pH and in acidic media due to protonation of the tertiary amine groups. Recently several research groups have described the synthesis of well-defined, near-monodisperse copolymers based on 2-(dimethylamino)ethyl methacrylate (DMA) via living polymerisation techniques. For example, Hoogeveen et al. described the synthesis and adsorption behaviour of a range of diblock copolymers comprising DMA and 2,3-dihydroxypropyl methacrylate (DHPM) [1]. These copolymers were prepared via classical anionic polymerisation using protecting group chemistry for the DHPM residues. It was found that these copolymers adsorbed onto silica particles via the basic DMA residues. Subsequent flocculation of the silica sol was explained in terms of charge neutralization of the anionic silica by the cationic DMA residues and the unexpectedly poor steric stabilization properties imparted by the DHPM block. The same workers also reported the use of such copolymers as stabilizers and flocculants for oxide particles [2] and compared the adsorption of DMA and quaternized DMA homopolymers onto colloidal silica and titania particles [3]. Creutz et al. described the controlled polymerisation of three basic monomers using classical anionic techniques: DMA [4], 4-vinylpyridine [5,6] and t-butylaminoethyl methacrylate [7]. Zwitterionic diblock and triblock copolymers comprising DMA and sodium methacrylate were also prepared, using t-butyl methacrylate as a protected monomer for the sodium methacrylate residues. The kinetics of unimer-micelle exchange of these naphthalene-labelled block copolymers, and also a series of related analogues, were studied by fluoresence spectroscopy using a pyrene probe [8,9]. The related DMA–ammonium methacrylate diblock copolymers were claimed to have some potential as universal pigment dispersants since a range of inorganic oxides and organic dyes could be readily dispersed in aqueous media over a wide pH range [10]. This was attributed to the ubiquitous adsorption characteristics imparted by the DMA residues.

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PII: S0032-3861(01)00066-0

We have had a long-standing interest in water-soluble block copolymers, particularly those based on DMA. In our initial studies, we prepared a series of DMA–MMA diblock copolymers [11] by group transfer polymerisation (GTP) and examined their efficacy as steric stabilizers in the dispersion polymerisation of styrene in alcoholic media [12]. The micellization behaviour of these hydrophilic–hydrophobic diblock copolymers in aqueous solution was studied using both static and dynamic light scattering (DLS) and analytical ultracentrifugation [13]. Thomas's group have recently published a series of neutron reflectivity studies of our selectively deuterated DMA–MMA copolymers adsorbed at the air–water interface [14–17].

More recently, we have focused on the synthesis and characterization of hydrophilic–hydrophilic, rather than hydrophilic–hydrophobic, block copolymers. For example, in a recent communication, [18] we described the block copolymerisation of DMA with 2-(diethylamino)ethyl methacrylate (DEA) by GTP. These copolymers exhibit strong pH-dependent surface activity and can form well-defined micelles in an aqueous solution. A detailed study of the pH-induced micellization of one of our DMA–DEA copolymers has been reported by Gast and co-workers [19]. Like Creutz et al., we have also prepared zwitterionic DMA–methacrylic acid diblock copolymers [20,21]. After exploring various protecting groups for the methacrylic acid residues, we found that 2-tetrahydropyranyl methacrylate was best suited for the synthesis of well-defined blocks since it was readily removed by acid hydrolysis under mild conditions. These copolymers dissolved molecularly in aqueous media at 20°C, but formed large micellar aggregates at elevated temperatures. They also behaved like synthetic proteins in that reversible precipitation occurs at a certain critical pH (the isoelectric point) in aqueous solution. Patrickios et al. [22,23] have exploited this phenomenon in order to isolate, and hence purify, natural proteins.

We have demonstrated that near-monodisperse DMA homopolymers [24] and DMA–alkyl methacrylate block copolymers [25,26] can be quantitatively derivatised under remarkably mild conditions using 1,3-propanesultone. In a later paper, [27] the remarkable selectivity of this reagent was also demonstrated. Thus the DMA residues of a DMA–DEA diblock copolymer could be quaternized exclusively, provided that the derivatization was carried out under mild conditions using a stoichiometric amount of the 1,3-propanesultone (although the DEA residues are more basic than the DMA residues they are actually much less reactive due to steric hindrance effects).

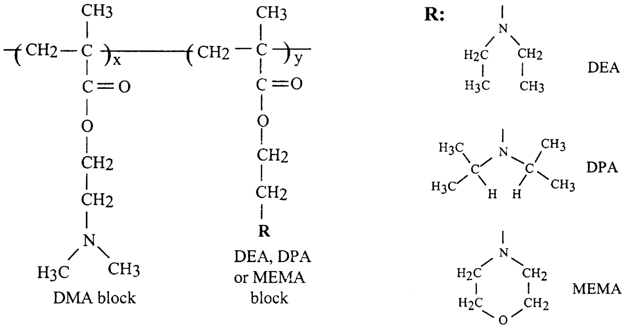

Fig. 1. General chemical structure of the tertiary amine methacrylate diblock copolymers.

In 1997, Nagasaki et al. reported that, contrary to conventional wisdom, heteroatom methacrylates such as DEA can be polymerised with good livingness using simple potassium alcoholate-based initiators in Tetrahydrofuran (THF) at or above room temperature [28]. We have extended this work to prepare styrene-functionalised macromonomers based on DMA and various other tertiary amine methacrylates [29]. These new well-defined macromonomers can be used as model reactive stabilizers to prepare polystyrene latexes via both aqueous emulsion and non-aqueous dispersion polymerisation. Furthermore, monomethoxy-capped poly(ethylene oxide) (MPEO) can be readily converted into the corresponding potassium alcoholate macro-initiator, which can be used to prepare novel MPEO–DMA diblock copolymers [30]. These copolymers, and their related analogues, are currently being evaluated as synthetic vectors for gene therapy applications [31].

In the present work, a wide range of near-monodisperse homopolymers and diblock copolymers based on four tertiary amine methacrylates, DMA, DEA, 2-(diisopropylamino)ethyl methacrylate (DPA) and 2-(*N*-morpholino)ethyl methacrylate (MEMA) were synthesized (see Fig. 1). The aqueous solubility, surface activity and micellization behaviour of these copolymers were studied using turbidimetry, surface tensiometry, ^{1}H NMR spectroscopy and DLS, respectively.

2. Experimental

2.1. Polymer synthesis

General. GTP was used to synthesize homopolymers and block copolymers with narrow molecular weight distributions and well-controlled molecular weights and comonomer compositions. All reactions were carried out under dry nitrogen. All chemicals were purchased from Aldrich, unless otherwise stated. All glassware and transfer needles were dried by storing in an oven overnight at 140°C before use. In order to eliminate surface moisture, all glassware was directly assembled from the oven, flamed out under high vacuum (10^{-4}–10^{-5} torr) and allowed to cool to room temperature. Nitrogen was passed through both silica and P_2O_5 drying columns prior to use. All monomers were passed down a basic alumina column to remove the hydroquinone methyl ether inhibitor.

2.1.1. Materials

Solvent: Tetrahydrofuran (THF; Fisons) was initially dried over sodium wire and refluxed over potassium for 3 days before use. The dried THF was stored over 4 Å molecular sieves at room temperature and transferred into the reaction vessel via cannula.

Monomers: DPA (Scientific Polymer Products), MEMA (Polysciences Inc.), DMA (Aldrich) and DEA (Aldrich) were each passed in turn through a basic alumina column, stirred over calcium hydride and 2,2-diphenyl-1-picrylhydrazyl hydrate (DPPH) inhibitor (except MEMA) and then stored at below 0°C. The monomers were each distilled under reduced pressure before being transferred into the reaction vessel by cannula under a dry nitrogen atmosphere.

Initiator: 1-Methoxy-1-trimethylsiloxy-2-methyl-1-propane (MTS) was distilled and stored at −5°C in a graduated schlenk flask under dry nitrogen prior to use.

Catalyst: Tetra-*n*-butyl ammonium bibenzoate (TBABB) was prepared by the method of Dicker et al. [32] and stored under dry nitrogen.

2.2. Synthesis of tertiary amine methacrylate homopolymers

To synthesize a homopolymer by GTP, the solid TBABB catalyst (approximately 10 mg, 2 mol% based on initiator) was added from a side arm under a nitrogen purge into a 250 ml three-necked round bottom flask. THF (100–150 ml) was then transferred into the flask via cannula before the addition of MTS (0.10–2.00 ml). This solution was stirred for 15 min and then monomer (typically 5–15 ml) was added dropwise by cannula. In the meantime, a contact thermocouple was attached to the side of the reaction vessel to monitor the exotherm during the addition of monomer. It was observed that the reaction temperature typically increased by 7–16°C. The reaction mixture was stirred until the solution temperature returned to room temperature (approximately 40–60 min). Then a 0.5 ml aliquot of the reaction mixture was extracted via syringe for GPC analysis. The reaction was quenched by adding methanol (2 ml) and then the solvent was removed by using a rotary evaporator. Finally, the recovered homopolymer was dried in a vacuum oven at 50–60°C for at least 2 days.

2.3. Synthesis of tertiary amine methacrylate diblock copolymers

To produce an AB diblock copolymer, the 0.5 ml aliquot was extracted from the reaction mixture (as described in Section 2.2) and then the second monomer (depending on the desired block copolymer composition) was added dropwise at an approximate rate of 1 ml min^{-1} via cannula and a second exotherm was recorded. The reaction mixture was stirred at room temperature until the exotherm had abated (approximately 60 min). After a further 0.5 ml aliquot was extracted for GPC analysis, the block copolymer was terminated with methanol (2 ml) prior to recovery using a rotary evaporator. The resulting polymer was dried in a vacuum oven at 50–60°C for 2 days. Copolymers of differing compositions were produced by changing the molar ratio of comonomers and different molecular weights were obtained by varying the comonomer/initiator ratio. All copolymerisations gave very high yields (>98%). In all block copolymerisations, the first polymerisation was carried out by using DMA as the first block and followed by the addition of either DEA, DPA or MEMA monomer.

2.4. Polymer characterization

2.4.1. Gel permeation chromatography (THF eluent)

Molecular weights and molecular weight distributions of all (co)polymers were determined by using gel permeation chromatography (GPC). The GPC set-up consisted of a Perkin Elmer LC pump and a RI detector, the columns used was either Mixed 'E' or Mixed 'D' (Polymer Labs), and calibration was carried out using PMMA standards (Polymer Labs), with M_n ranging from 680 to 53 000 g mol^{-1}. The GPC eluent was HPLC grade THF stabilized with BHT, at a flow rate of 1 ml min^{-1}.

2.4.2. Nuclear magnetic resonance spectroscopy (NMR)

The compositions of all block copolymers and their micellization behaviour in water were investigated using either Bruker AC-P 250 or 300 MHz instruments and either $CDCl_3$ or D_2O/NaOD or D_2O/DCl solvents. The block copolymer compositions were determined by comparing appropriate integrals assigned to the different comonomers (see Section 3). In addition, the number-average molecular weights of selected DMA and DEA homopolymers were calculated from their NMR spectra using the three methoxy protons of the MMA residue derived from the MTS initiator as an end-group.

2.4.3. Turbidimetry

A PC-controlled Perkin Elmer Lambda 2S UV/VIS spectrometer was used to assess both the effect of homopolymer molecular weight on the cloud points and the effect of varying the copolymer composition in the DMA–MEMA block copolymers ($M_n = 5000$ g mol^{-1}). An aqueous solution of the (co)polymer (2.5 ml, 1 w/v%) was transferred to a 10 mm path length quartz cuvette containing a stir bar. A small temperature probe was immersed in the upper part of the stirred copolymer solution and the solution temperature was increased slowly from 20 to 65°C. The optical density at 500 nm and the temperature were monitored simultaneously.

2.4.4. Hydrogen ion titration

In order to determine the pK_a values for the conjugate acids of the four tertiary amine methacrylate homopolymers a 0.5% homopolymer solution at pH 2 was titrated using 0.5–1.0 M KOH solution. Solution pH was monitored using a Corning Check-Mite pH sensor. Calibration was carried out using pH 4, 7 and 10 buffers.

2.4.5. Dynamic light scattering (DLS)

The intensity-average hydrodynamic micelle diameters of the block copolymers in aqueous solution were measured using a Malvern PCS 4700 spectrometer equipped with a 80 mV argon ion laser operating at $\lambda_o = 632.8$ nm and a series 7032 Multi-8 Correlator. The measurements were performed at a fixed angle of 90° and data were fitted using both monomodal cumulants analysis and the CONTIN algorithm. All measurements were carried out using 1 w/v% solutions. The solution temperature was controlled to within ±0.1°C.

2.4.6. Surface tensiometry

The surface tension measurements were carried out using a Kruss K10ST surface tensiometer (platinum ring method) for both homopolymers and block copolymers.

3. Results and discussion

3.1. Homopolymer synthesis

GTP was used to synthesize a series of each of the DMA, DEA and MEMA homopolymers for aqueous solubility studies. The molecular weights of the DMA homopolymers ranged from 1×10^3 to 5×10^4 g mol^{-1}. The molecular weights of both the DEA and the MEMA homopolymers ranged between 1×10^3 and 3×10^4 g mol^{-1}. Only one DPA homopolymer was synthesized; it had a molecular weight of 4800 g mol^{-1} (see Table 1). Typical ^{1}H NMR spectra of these four tertiary amine methacrylate homopolymers are shown in Fig. 2, recorded in $CDCl_3$ with the relevant signals labelled.

The number-average molecular weights (M_n) and the polydispersities (PD) of the homopolymers were determined by GPC and are summarized in Table 1. In general, reasonable agreement was observed between the theoretical and the observed M_n, as determined by GPC in THF. All homopolymers had low PD's (<1.20), which is typical of polymers synthesized via GTP [33]. The observed small increases in M_n compared to theoretical values are almost certainly due to the fact that the hydrodynamic volumes of the tertiary amine methacrylate (co)polymers in THF are different to those of the PMMA calibration standards. ^{1}H NMR spectroscopy was used to determine the absolute M_n's of selected DMA and DEA homopolymers by comparing the peak integral of the three methoxy protons in the terminal MMA residue derived from the MTS initiator, at δ 3,6 (see Fig. 2) with the oxymethylene protons of the DMA or DEA residues at δ 4.0. The molecular weight data obtained from NMR (see Table 2) was in generally good agreement with the GPC data.

Table 1
Number-average molecular weights, PD and aqueous solution properties of the four tertiary amine methacrylate homopolymers investigated in this study

Sample code	Homopolymer type	Mn (theory) (g mol^{-1})	Mn (exp.) (g mol^{-1})[a]	PD[a]	Cloud point (°C)[b]	Limiting surface tension (mN/m)[c]
VB32D	DMA	950	1450	1.16	46.4	37.2
VB32C	DMA	1150	1600	1.17	46.6	39.6
VB81	DMA	3450	3350	1.12	44.9	41.8
VB84	DMA	5050	4750	1.14	43.2	42.2
VB83	DMA	6320	6150	1.11	40.7	42.4
VB32E	DMA	10 100	12 450	1.07	38.3	42.7
VB30B	DMA	15 150	32 000	1.04	34.5	42.6
VB30A	DMA	24 650	53 000	1.14	32.2	42.8
VB35A	MEMA	1200	1750	1.22	53.4	–
VB35B	MEMA	2500	2650	1.25	49.0	–
VB27	MEMA	5350	4950	1.10	46.2	–
VB35C	MEMA	10 600	12 100	1.08	41.2	–
VB35D	MEMA	21 350	24 450	1.07	36.3	–
VB189	MEMA	31 000	32 000	1.13	34.0	–
VB48	DEA	3100	3550	1.18	insol	–
VB50	DEA	4200	4350	1.16	insol	–
VB51	DEA	5850	5650	1.11	insol	–
VB49	DEA	9700	11 000	1.06	insol	–
VB52	DEA	14 000	15 000	1.06	insol	–
VB53	DEA	18 650	21 500	1.06	insol	–
VB54	DEA	24 250	33 700	1.05	insol	–
VB77	DPA	4200	4800	1.12	insol	–

[a] As determined by GPC (calibrated with poly(methyl methacrylate) standards).

[b] As determined by turbidimetry.

[c] As determined by surface tensiometry on 0.5 w/v% polymer solutions at 20°C.

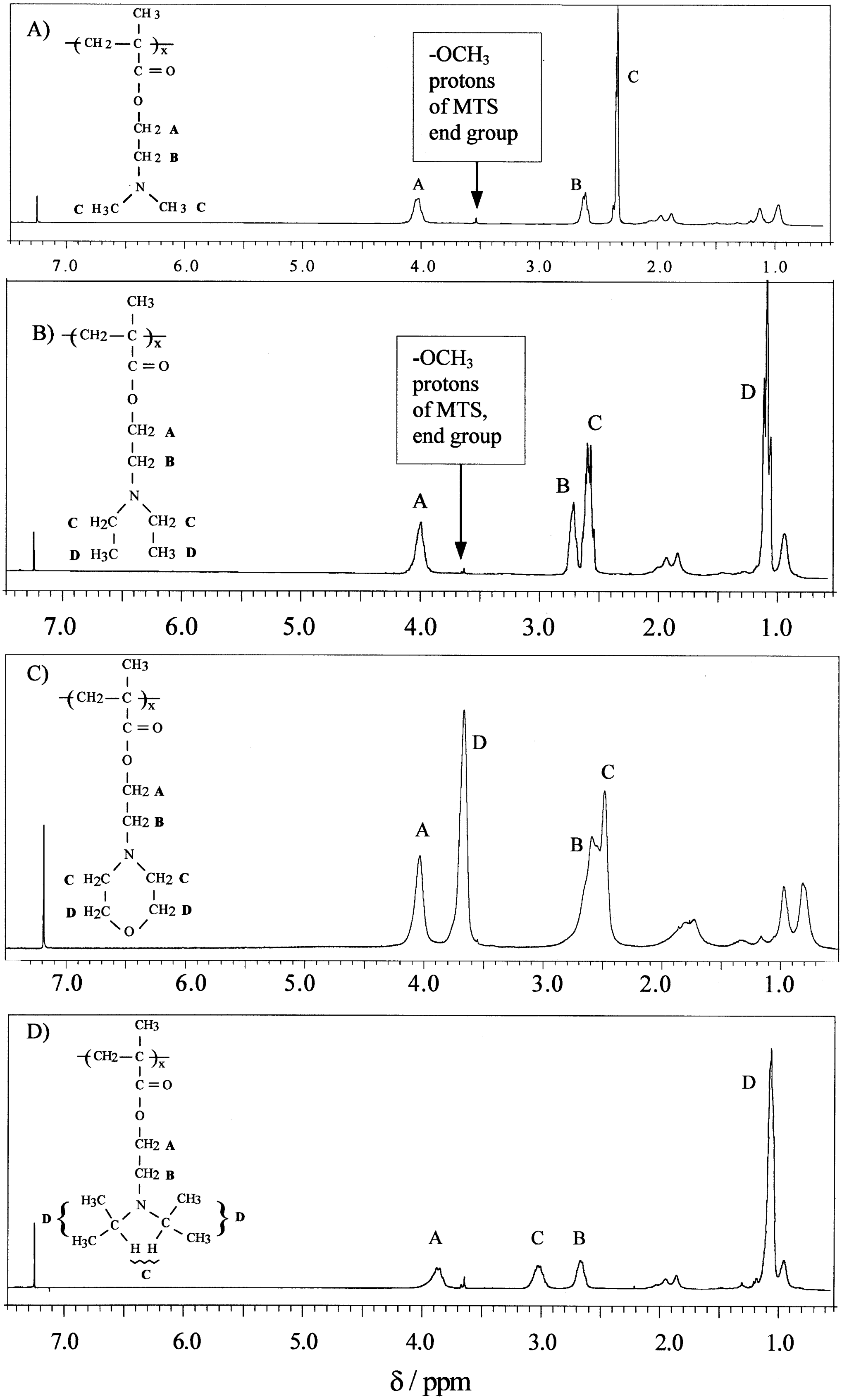

Fig. 2. Typical ^{1}H NMR (CDCl$_3$) spectra of (a) DMA homopolymer, $M_n = 6150$ g mol^{-1}; (b) DEA homopolymer, $M_n = 5650$ g mol^{-1}; (c) MEMA homopolymer, $M_n = 32\ 000$ g mol^{-1} and (d) DPA homopolymer, $M_n = 4800$ g mol^{-1}.

Table 2
Molecular weight data of the DMA and DEA homopolymers, determined using GPC and NMR (end-group analysis based on the MTS initiator)

Sample code	Homopolymer type	M_n (theory) (g mol^{-1})	M_n (GPC) (g mol^{-1})	M_n (NMR) (g mol^{-1})	PD
VB291A	DMA	5000	5 740	5350	1.12
VB291B	DMA	10 000	11 700	10 100	1.07
VB291C	DMA	17 000	21 300	21 350	1.09
VB50	DEA	4200	4350	5500	1.16
VB52	DEA	14 000	15 000	16 750	1.06

3.2. Aqueous solution properties of the homopolymers

The DMA and MEMA homopolymers are both weak polybases which are water-soluble at both neutral and acidic pH at room temperature. However, they precipitate from neutral or basic aqueous solutions at 32–53°C, depending on their molecular weight (see Fig. 3). When the solution is cooled, the polymer becomes soluble again. This thermo-reversibility has been observed by many researchers with different neutral polymers based on methyl vinyl ether (MVE), methyl triethylene glycol vinyl ether (MTEGVE), isopropylacrylamide, ethylene oxide etc. For example, Forder et al. [34] reported temperature-induced micellization using an MTEGVE–MVE diblock copolymer. In this system the difference between the cloud points of the two blocks is around 30–40°C, with the MVE block being less hydrophilic. As the solution temperature increases, this block becomes partially dehydrated and forms micelle cores while the MTEGVE block remains solvated. It was expected that DMA–MEMA block copolymers would show similar behaviour, despite the relatively small differences between the cloud points of the two blocks. However, Lowe [35] reported that no well-defined micelles were formed: only large aggregates of ~650 nm were observed above 40°C.

In the present work, we focused on exploiting the subtle differences in basicity and hydrophilicity between the tertiary amine methacrylate blocks. As can be seen in Fig. 3, the cloud points of DMA and MEMA homopolymers increased monotonically with decreasing degrees of polymerisation (see Table 1). This trend was expected since, in the lower limit, the DMA and MEMA monomers are water-miscible at all temperatures. For low degrees of polymerisation ($D_p < 105$), MEMA homopolymers are more hydrophilic than DMA homopolymers. The cloud point of MEMA homopolymer falls from 53.4°C at a degree of polymerisation of approximately 9, to 32°C at a degree of polymerisation of 156. Similarly, for DMA homopolymers, the cloud point varies from 46.4°C for a degree of polymerisation of 9, down to 32.2°C for a degree of polymerisation of 337. Tong et al. [36] have observed similar molecular weight effects on the cloud point of poly(*N*-isopropylacrylamide).

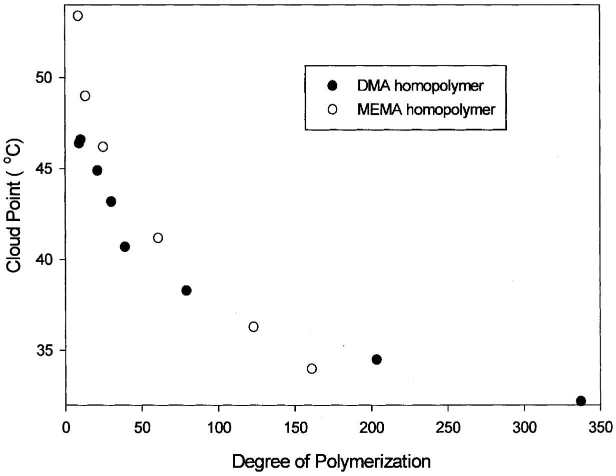

Fig. 3. Effect of the degree of polymerisation on the cloud points for a series of DMA homopolymers at pH 8, and MEMA homopolymers at pH 7 (1.0 w/v% solution).

In addition, MEMA homopolymers are more soluble at high pH (at room temperature) than DMA homopolymers at 20°C. Increasing the solution pH from pH 8 to 10 also slightly decreases the cloud points of both homopolymers. It was also observed that MEMA homopolymer can be precipitated (salted out) relatively easily from aqueous solution on addition of electrolytes such as Na_2SO_4, K_2CO_3, Na_3PO_4 etc. However, MEMA homopolymer can be redissolved as a cationic polyelectrolyte by the addition of acid even in the presence of high salt concentration due to protonation of the morpholine groups.

In contrast, it was observed that the DEA and the DPA homopolymers were both completely insoluble in aqueous media at both neutral and basic pH. This is due to the increasing hydrophobicity of the alkyl substituents on the tertiary amino nitrogen atom. However, these latter homopolymers both dissolved readily in acidic aqueous solution (pH 3–4) due to protonation of the tertiary amine groups.

The surface tension data for 1.0 w/v% DMA homopolymer solutions show that their limiting surface tensions slightly decrease from 43 to 37 mN m^{-1} as the molecular weight is decreased from 53000 to 1450 (see Table 1). This decrease may be partly due to a chain-end effect, the first unit in the polymer chain is MMA, derived from the MTS initiator and is relatively hydrophobic.

The titration curves shown in Fig. 4 were obtained by dissolution (1.5×10^{-2} M, based on tertiary amine residues) of each of the DMA, DEA, DPA and MEMA homopolymers in turn at pH 2 and then monitoring the pH as

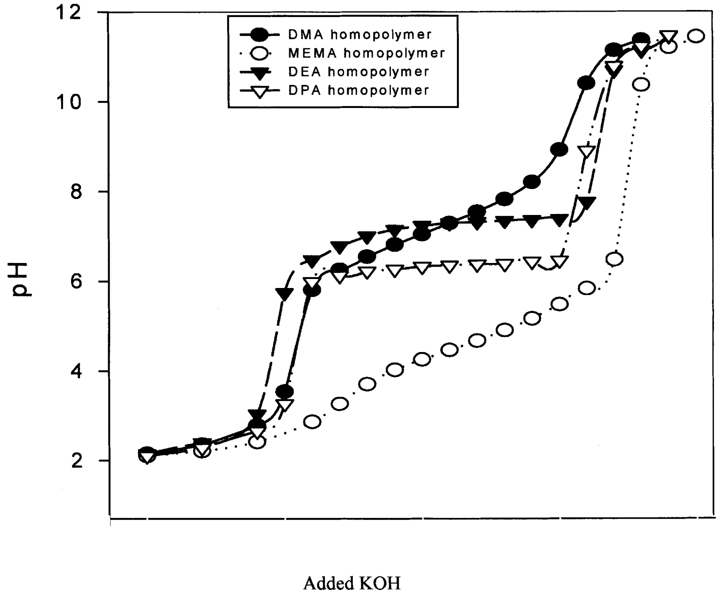

Fig. 4. Titration curves of the four tertiary amine methacrylate homopolymers at 20°C (1.5×10^{-2} M tertiary amine residues-based polymer solution).

KOH was gradually added. From these titration curves, pK_a values of 7.0, 7.3, 6.0 and 4.9 were obtained for the conjugate acid forms of the tertiary amine methacrylate residues in the DMA, DEA, DPA and MEMA homopolymers, respectively. The measured pK_a of 7.0 for DMA homopolymer agrees well with pK_a values reported in the literature [1,37,38]. The stronger basicities (weaker acidity for the corresponding conjugate acids) of the DEA and DPA homopolymers agree well with small-molecule analogs [39–41]. For example, the pK_a of the conjugate acid of trimethylamine is 9.74, and the pK_a of the conjugate acid of diethylmethylamine is 10.43. According to our titration data, the pK_a for DEA homopolymer is comparable to that of DMA homopolymer as expected, whereas the p**K**$_a$ of the DPA homopolymer is somewhat lower. The lower basicity of the DPA homopolymer is presumably due to the increased steric congestion at the nitrogen atom compared with DMA homopolymers. For the DEA homopolymer the competing effects of higher basicity and increased steric hindrance leave the pK_a almost unchanged relative to DMA homopolymer. On the other hand, MEMA homopolymer has a very low pK_a of 4.9. Again, there is a small molecule precedent: the conjugate acid of morpholine has a pK_a of only 8.33 whereas diethyl amine has a pK_a of 10.98 [35,36].

Most conjugate acids of small-molecule tertiary amines have pK_a values of around 10. Obviously, this is not the case for our polymers, which behave as weak polybases. Hoogeveen et al. [1] titrated both DMA monomer and DMA homopolymer and found a pK_a of around 7 for the latter, which is excellent agreement with our value. They concluded that the relatively low pK_a of DMA homopolymer is due to two effects: First, the intrinsic pK_a of the tertiary amine group in DMA monomer is 8.4, which is rather lower than expected. This unusually low pK_a has been attributed to intra-molecular cyclization by Pradny and Sevcik, who suggested that the amine group forms a cyclic structure with the carbonyl group in the side chain, thus lowering the effective basicity [37]. Second, the polymer chains resist the local build-up of cationic charge density so that it becomes progressively harder to protonate the remaining neutral amine groups.

The pK_a values of the block copolymers lie between the pK_a's of the related homopolymers, as expected. The DEA and DPA homopolymers precipitated from aqueous solution when the solution pH exceeded the pK_a due to their decreased degree of protonation, and hence increasing hydrophobicity. In view of these observations, we anticipated that diblock copolymers based on these tertiary amine methacrylates should exhibit interesting micellization behaviour at different solution pH and/or different temperature. Thus, the DMA monomer was block copolymerized in turn with the other three monomers, DPA, MEMA and DEA.

3.3. Tertiary amine methacrylate block copolymers

3.3.1. Synthesis

A series of each of the DMA–DEA, DMA–MEMA and DMA–DPA diblock copolymers (see Fig. 1) was successfully synthesized in high yields using GTP. Either the comonomer compositions were varied while the overall molecular weight was kept approximately constant, or the copolymer M_n was varied while the comonomer composition was kept constant. All polymerisations were carried out by first polymerising DMA monomer, followed by the second monomer (either DEA, DPA or MEMA). In most cases, GTP indicated little or no homopolymer contamination. In the occasional case of significant contamination, the

Table 3
Copolymer compositions, number-average molecular weights, PD and cloud-points for the DMA–DEA, DMA–MEMA and DMA–DPA diblock copolymers

Sample code	Block copolymer type	DMA content (theory) (mol%)	DMA content[a] (mol%)	M_n (theory) (g mol^{-1})	M_n (exp.) (g mol^{-1})[b]	PD[b]	Cloud point (°C)[c]
VB66	DMA–DEA	80	78	10 400	12 400	1.10	–
VB61	DMA–DEA	74	72	8950	11 350	1.10	–
VB88	DMA–DEA	70	67	9500	11 050	1.10	–
VB65	DMA–DEA	68	67	18 900	21 600	1.09	–
VB89	DMA–DEA	60	61	11 300	13 700	1.10	–
VB90	DMA–DEA	50	50	13 800	15 000	1.10	–
VB70	DMA–DEA	49	49	10 600	9550	1.15	–
VB69	DMA–DEA	35	36	9850	13 600	1.09	–
VB71	DMA–DEA	22	24	9850	9500	1.10	–
VB28A	DMA–MEMA	80	82	4450	5950	1.10	40.6
VB28C	DMA–MEMA	50	48	5050	5100	1.14	42.8
VB28E	DMA–MEMA	20	21	5100	6000	1.08	43.6
VB43	DMA–MEMA	86	85	35 350	45 600	1.13	32.7
VB41	DMA–MEMA	67	65	15 450	19 200	1.10	36.3
VB36	DMA–MEMA	60	59	27 950	31 100	1.08	34.1
VB33A	DMA–MEMA	50	48	19 200	21 550	1.11	35.1
VB190	DMA–MEMA	38	40	25 000	27 600	1.09	33.5
VB37A	DMA–MEMA	40	38	17 700	33 000	1.17	32.6
VB37	DMA–MEMA	34	35	17 700	36 000	1.10	33.0
VB85	DMA–DPA	82	80	8150	11 500	1.10	–
VB80A	DMA–DPA	72	72	9650	12 050	1.12	–
VB86	DMA–DPA	60	61	12 050	15 750	1.11	–

[a] As determined by ^{1}H NMR spectroscopy.
[b] As determined by GPC (calibrated with poly(methyl methacrylate) standards).
[c] As determined by turbidimetry.

block copolymers were precipitated from THF into either *n*-hexane (e.g. the DMA–MEMA diblock due to the insolubility of the MEMA block in n-hexane) or water at pH > 8 (e.g. DMA–DEA and DMA–DPA diblocks). Copolymer M_n's and PD were determined by GPC and are summarized in Table 3. In general, good agreement was observed between the theoretical molecular weights and the GPC values. All diblock copolymers had PD lower than 1.20.

3.3.2. Determination of block compositions

Block compositions were determined by ^{1}H NMR spectroscopy (see Table 3) and good agreement with the expected compositions was observed. Compositions were determined by comparing well-defined peak integrals assigned to the different comonomers. For example, the ^{1}H NMR spectrum in Fig. 5A represents a DMA–DEA diblock copolymer (VB65). The peak integral C of the six dimethylamino protons in the DMA residues at δ 2.3 was compared to that of the oxymethylene protons in the DEA residues at δ 4.0. The DMA content was determined to be 67 mol%, which compares well with the theoretical DMA content of 68 mol%.

Similarly, the ^{1}H NMR spectrum in Fig. 5B represents a DMA–DPA diblock copolymer (VB86). Its block copolymer composition was determined by comparing the peak integral C due to the DMA residues at δ 2.3 with the two methine protons of the diisopropyl groups in the DPA residues at δ 3.0. The DMA content was determined to be 61 mol%, which compared well with the theoretical DMA content of 60 mol%.

Finally, the ^{1}H NMR spectrum in Fig. 5C represents a DMA–MEMA diblock copolymer (VB190). The peak integral of the DMA residues at δ 2.3 was compared to that of the four oxymethylene protons in the morpholine groups of the MEMA residues at δ 3.7. The DMA content was found to be 40 mol%, which compared well with the theoretical DMA content of 38 mol%.

3.3.3. Aqueous solution properties

Although structurally very similar to DMA, the DEA and DPA monomers are both immiscible in water at neutral pH and both DEA and DPA homopolymers are completely insoluble at neutral (or basic pH) at room temperature. On the other hand, molecular dissolution (as weak cationic polyelectrolytes) occurs in acidic media due to the protonation of the tertiary amine residues; reversible precipitation occurs on addition of base. In contrast, DMA homopolymer is water-soluble at room temperature up to pH 8–10. In view of these subtle solubility differences we anticipated that both DMA–DEA and DMA–DPA diblocks should exhibit pH-induced micellization since both types of copolymers behave as hydrophilic–hydrophilic diblocks in acidic solution and hydrophilic–hydrophobic diblocks in basic solution. One of the problems in studying the micellization behaviour of conventional hydrophilic–hydrophobic block

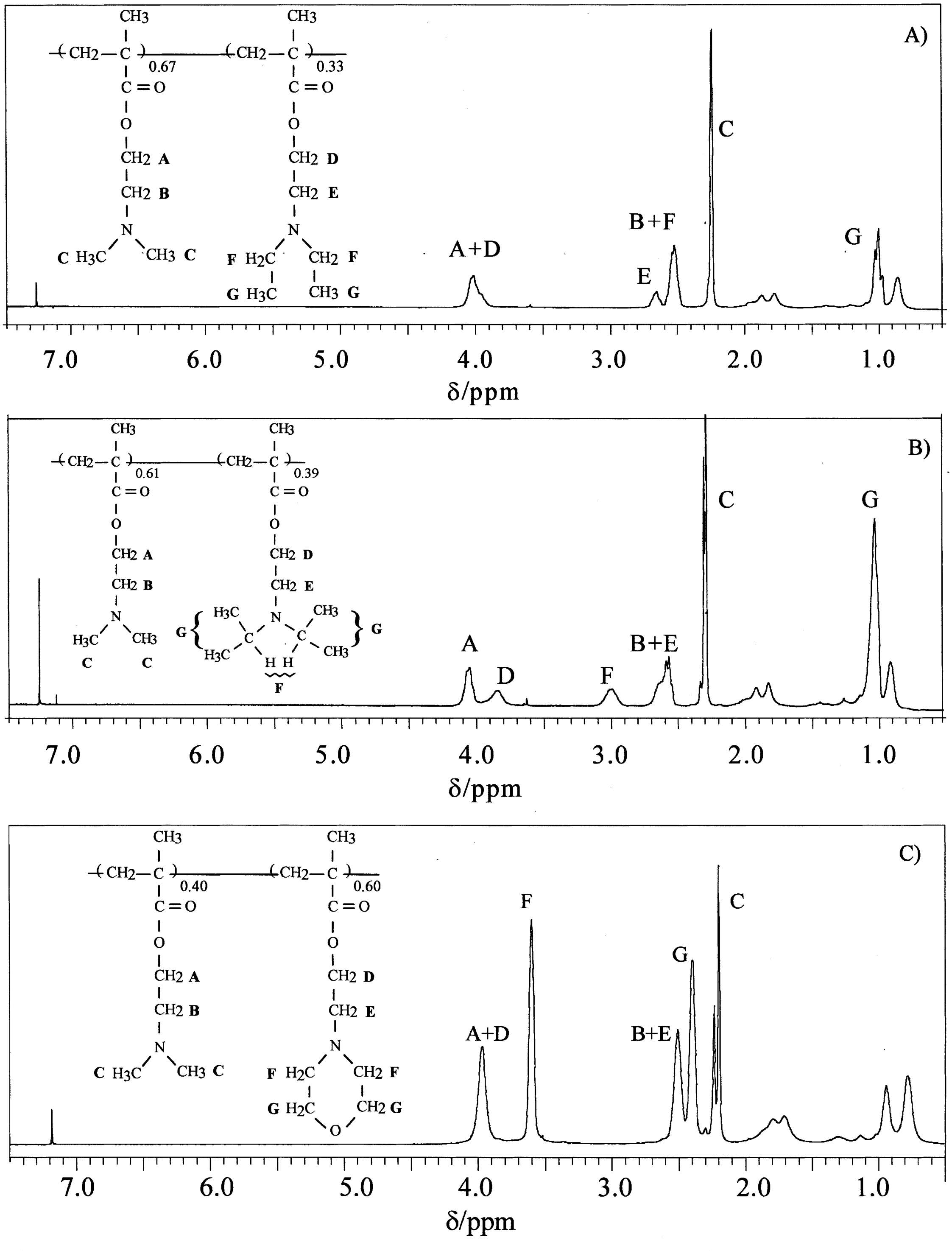

Fig. 5. Typical ^{1}H NMR (CDCl$_3$) spectra of (A) a 67:33 DMA–DEA diblock copolymer, $M_n = 21\,600$ g mol^{-1}; (B) a 61:39 DMA–DPA diblock copolymer $M_n = 15\,750$ g mol^{-1}; (C) a 40:60 DMA–MEMA diblock copolymer, $M_n = 27\,600$ g mol^{-1}.

copolymers is that water-miscible co-solvents (THF, alcohols, DMF etc.) are normally required for true molecular dissolution in aqueous solution prior to micellization. In our micellization studies, no co-solvent was required. The tertiary amine methacrylate diblock copolymers were simply dissolved molecularly in either neutral or acidic aqueous media and the solution pH was then increased above the critical micellization pH of the copolymer in order to form micelles. Under these conditions, the hydrophilic DMA block forms the micelle corona and the hydrophobic DEA or DPA block forms the micelle core (see Fig. 6).

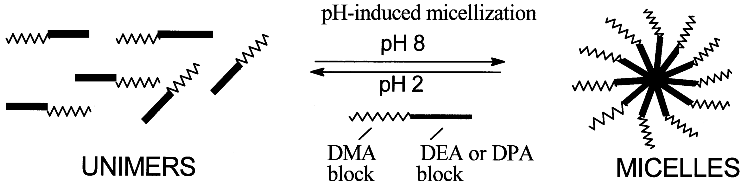

Fig. 6. Schematic representation of pH-induced micellization for both DMA–DEA and DMA–DPA diblock copolymers.

3.4. DMA–DEA block copolymers.

It was observed that, if the DMA content is greater than approximately 50 mol%, DMA–DEA diblocks can be dispersed directly into water at around neutral pH to form micelles of between 10 and 60 nm, depending on the block composition. DEA-rich block copolymers (>55–60 mol% DEA) are insoluble under these conditions.

Examination of all molecularly dissolved DMA–DEA diblock copolymer solutions (1.0%) at pH 2 by DLS confirmed very weak light scattering in all cases. However, adjusting the solution pH to above the critical micellization pH produced much more intense light scattering due to formation of micelles of 17–62 nm diameter with relatively narrow size distributions (see Table 4). Micellization of all DMA–DEA block copolymers occurred between pH 7–9, depending on the comonomer composition and temperature. The micelle diameters of the 50:50 DMA–DEA blocks increased from 25 to 50 nm at around pH 8 with increasing molecular weight (see Table 4). Micelle diameters also increase with increasing DEA content for a given molecular weight. Micellization proved to be completely reversible: the subsequent addition of acid resulted in complete dissolution of the micelles.

Initially the 50:50 DMA–DEA block copolymer was molecularly dissolved in DCl–D_2O (see Fig. 7A). On addition of NaOD, the strong signal at δ 1.3 observed in Fig. 7A due to the six equivalent methyl protons of the DEA residues completely disappears in Fig. 7B, indicating that this deprotonated block sequence is no longer solvated at pH 7.9. This is strong evidence for the DEA block forming hydrophobic micellar cores, as expected.

Surface tension vs pH curves for three DMA–DEA block copolymers (containing 78, 72 and 61 mol% DMA, respectively) are shown in Fig. 8A. As the solution pH is increased, the diblock becomes strongly adsorbed at the air–water interface, thus lowering the surface tension of the solution. Above pH 8, the limiting surface tension of this solution is approximately 32–33 mN m^{-1} for the copolymers containing 78 or 72 mol% DMA and 37 mN m^{-1} for the 61:39 DMA–DEA block copolymer. These limiting surface tensions are similar to that obtained with small molecule surfactants but relatively low compared to most other synthetic water-soluble block copolymers. For example, Baines et al. [10] reported that the limiting surface tension obtained for a 1.0% aqueous solution of a DMA–MMA diblock copolymer of comparable molecular weight was only 46 mN m^{-1}. Similarly, a surface tension plateau of ca. 42 mN m^{-1} was observed by Teyssie and co-workers [42] for a sulfonated glycidyl methacrylate–MMA block copolymer with a similar hydrophilic–hydrophobic balance.

It is also possible to identify the so-called critical micelle concentration (CMC) by determining the concentration dependence of the surface tension of a block copolymer.

Table 4
A summary of the hydrodynamic diameters, PD and solubilities for two series of DMA–DEA and DMA–DPA diblock copolymers at 20°C

Sample code	Block copolymer type	DMA content[a] (mol%)	M_n (exp.) (g mol^{-1})[b]	Solution pH	Micelle diameter (nm)[c]	PD[c]	Aqueous solubility[d]
VB66	DMA–DEA	78	12 400	9.0	17	0.240	yes
VB61	DMA–DEA	72	11 350	9.0	19	0.090	yes
VB89	DMA–DEA	61	13 700	8.6	26	0.066	yes
VB70	DMA–DEA	49	9550	8.1	25	0.106	yes
VB90	DMA–DEA	50	15 000	8.2	32	0.057	slow
VB120	DMA–DEA	51	32 600	8.1	50	0.099	very slow
VB119	DMA–DEA	34	35 000	7.5	62	0.074	No
VB71	DMA–DEA	24	9500	7.5	ppt.	–	No
VB85	DMA–DPA	80	11 500	9.3	18	0.170	yes
VB80A	DMA–DPA	72	12 050	8.0	23	0.116	slow
VB86	DMA–DPA	61	15 750	6.7	40	0.067	No

[a] As determined by ^1H NMR spectroscopy.

[b] As determined by GPC.

[c] As determined on 1.0 w/v% copolymer solutions by DLS at 25°C.

[d] Dissolution attempted in de-ionized water at 20°C.

Fig. 8b shows the surface tension curves of the DMA–DEA block copolymers with three different comonomer compositions. The CMC for a 61:39 DMA–DEA block copolymer is estimated to be 0.025 w/v%, which is slightly higher than the CMC's of around 0.020 w/v% for the 72:28 or 78:22 DMA–DEA block copolymers. Again, these latter CMC's are lower than those reported for hydrophilic–hydrophobic DMA–MMA diblock copolymers of comparable molecular weight and block composition synthesized by Baines et al. [11].

3.5. DMA–DPA block copolymers

In order to characterize the aqueous solution behaviour of the DMA–DPA block copolymers, DLS and ^1H NMR spectroscopy studies were performed at 20°C. First, 1.0 w/v% solutions of the 61:39, 72:28 and 80:20 DMA–DPA block copolymers were prepared in turn using the same procedure used for the DMA–DEA diblocks. Micelles with DPA cores were obtained by careful adjustment of the solution pH. The diblock copolymer dissolved molecularly in dilute HCl at pH 2. Careful addition of KOH to this acidic solution produced a final pH between 6.7 and 9.3, depending on the block composition (see Table 4). Under these conditions, the DPA block is substantially deprotonated and therefore hydrophobic, while the DMA block remains solvated. Thus, micelles comprising DPA cores and DMA coronas are expected, as shown schematically in Fig. 6. Proton NMR studies confirm this

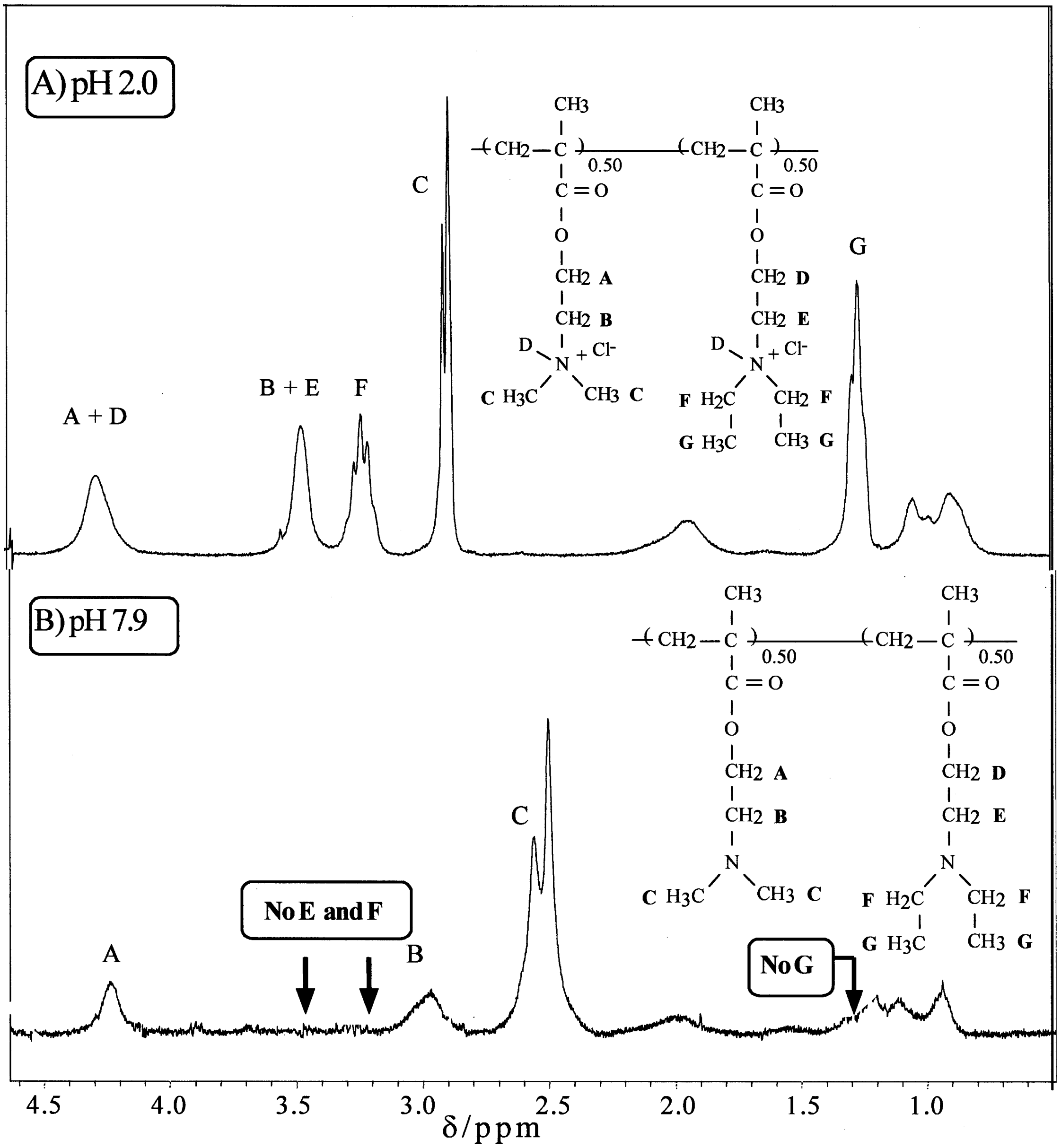

Fig. 7. ^1H NMR (D_2O) spectra of a 50:50 DMA–DEA block copolymer, $M_n = 15\ 000\ g\ mol^{-1}$; (A) at pH 2, (B) at pH 7.9.

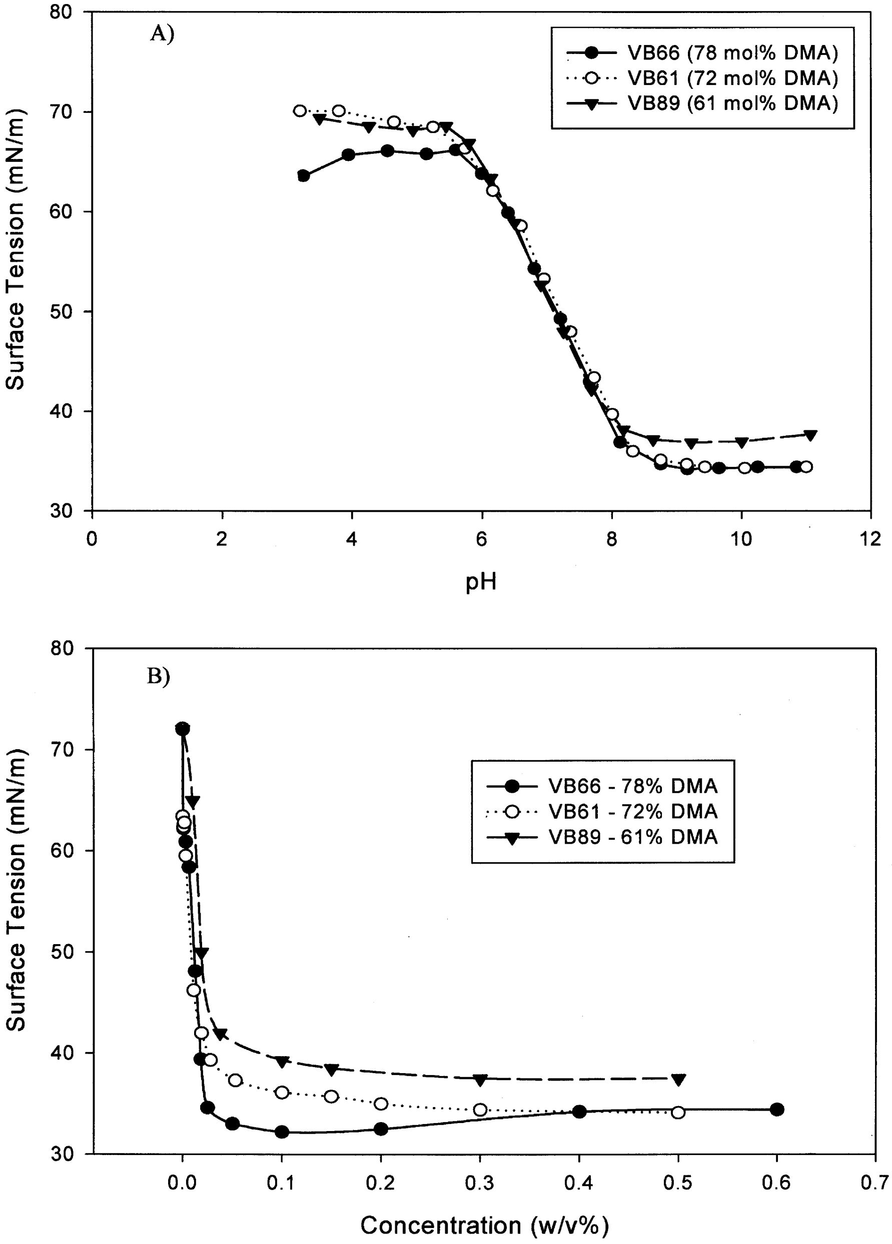

Fig. 8. Variation of surface tension with (A) solution pH for 0.2 w/v% aqueous solutions of the 78:22, 72:28 and 61:39 DMA–DEA block copolymers (M_n 12 400, 11 350 and 13 700 g mol^{-1}, respectively); (B) surface tension curves for the same three block copolymers as a function of copolymer concentration at pH 8.

to be the case. The ^{1}H NMR spectra of the 61:39 DMA–DPA diblock copolymer in D_2O recorded at different solution pH are shown in Fig. 9. Both blocks are soluble at pH 2 due to protonation of the tertiary amine residues and therefore signals due to both DMA and DPA residues are visible in Fig. 9A. As the solution pH is increased to pH 7, the signals due to the DMA residues remain prominent, whereas the disappearance of the signals due to the DPA residues at δ 1.4 and δ 3.8 in Fig. 9B indicates substantial dehydration and reduced mobility of this block. This is strong evidence for the DPA blocks forming hydrophobic micelle cores, the DMA blocks forming the hydrated micelle corona.

DLS studies indicated micelles with intensity-average micelle diameters of between 18–40 nm at 20°C depending on the block composition (see Table 4). The diameter increases with increasing DPA content. In addition, the micelle size distribution becomes narrower as the DPA content increases. In general, PD of <0.10 indicate near-monodisperse micelles. As the DPA content of the DMA–DPA diblock copolymer is increased, micellization occurs at lower pH. Addition of acid led to reprotonation of the DPA residues, and unimers were again produced at pH 2–4. In addition, the critical micellization pH for the DMA–DPA block copolymer is lower than that of a DMA–DEA diblock copolymer of similar molecular weight and DMA content (compare entries VB89 and VB86 in Table 4). This is due to the more hydrophobic character and relative ease of deprotonation of the sterically congested DPA residues in the DMA–DPA diblock copolymer. It was also observed that when the DMA content of the copolymer is greater than approximately 65 mol% these DMA–DPA block copolymers can be dispersed directly into water at around neutral pH to form micelles of between 18–23 nm, depending on the block composition.

3.6. DMA–MEMA block copolymers

From Fig. 3 it is clear that, for degrees of polymerisation less than 60, MEMA homopolymer is slightly more hydrophilic than DMA homopolymer. Thus DMA–MEMA diblock copolymers might be expected to exhibit temperature-induced micellization just above the cloud-point of

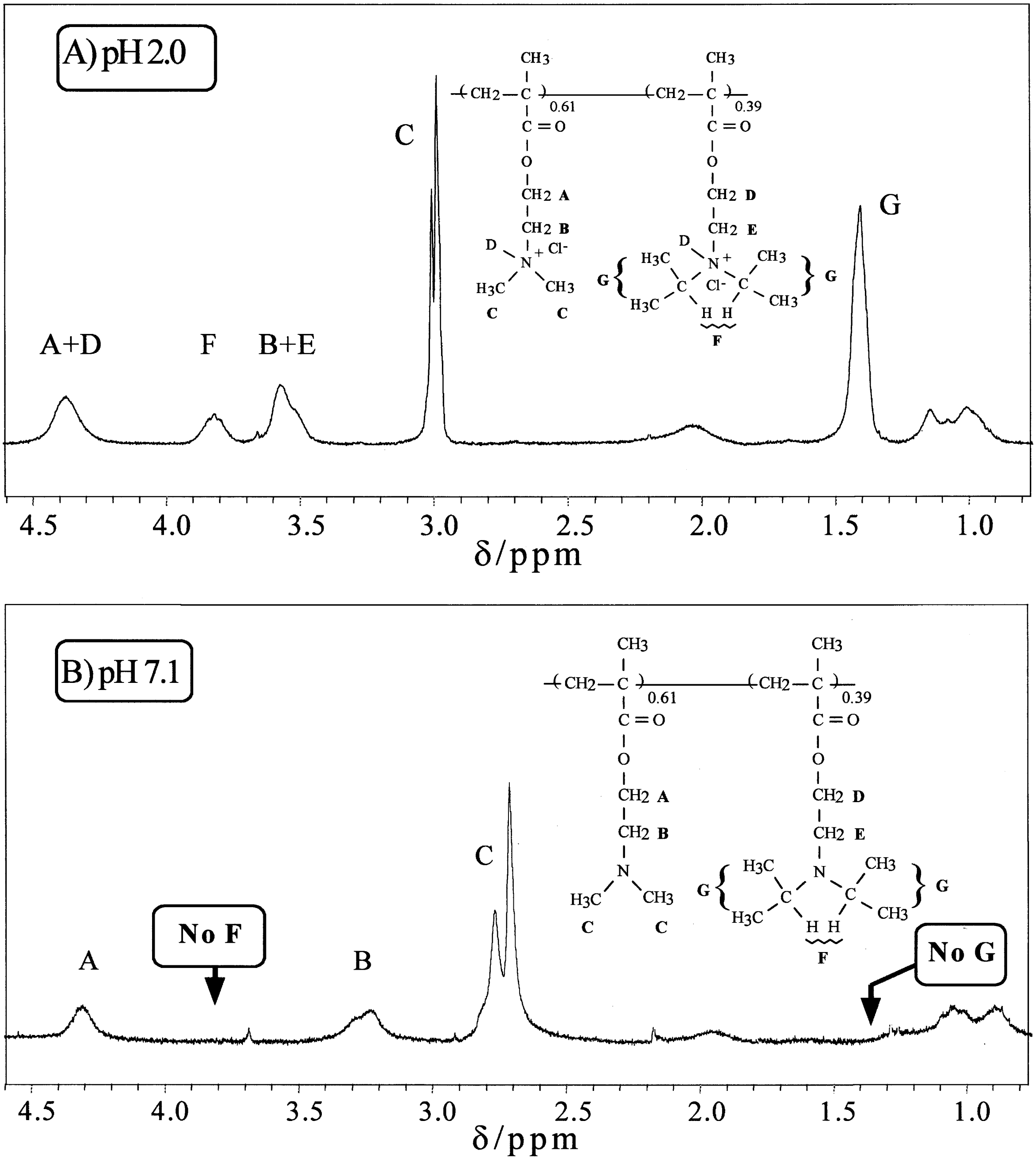

Fig. 9. ^{1}H NMR spectra of a 61:39 DMA–DPA block copolymer in D_2O (M_n = 15 750 g mol^{-1}), (A) at pH 2.0, (B) pH 7.1. Note the disappearance of the signals due to the DPA residues at pH 7.1, indicating that this block forms the dehydrated micelle cores.

the DMA block, with the still-solvated MEMA chains forming the micelle coronas. However, in a preliminary study [35] Lowe found that well-defined micelles were not obtained; DMA–MEMA diblocks merely formed ill-defined, polydisperse aggregates prior to macroscopic phase separation. This was attributed to the small difference between the cloud-points of the DMA and MEMA blocks.

In the present work, we demonstrate that it is possible to form well-defined micelles from DMA–MEMA diblocks. However, these micelles have MEMA cores and DMA coronas, rather than the DMA cores and MEMA coronas originally anticipated. This was achieved by the subtle variation of solution pH and added salt in order to discriminate between the DMA and MEMA blocks in terms of their relative hydrophilicity. Protonation of the tertiary amine groups occurs between pH 4–6 for MEMA residues (pK_a 4.9) and between pH 6–8 for DMA residues (pK_a 7.0) (see Fig. 4). These subtle differences in basicity allow selective protonation of the DMA block at pH > 6. It was observed that lowering the solution pH from pH 8 to 7 increased the cloud point of the DMA homopolymer to above 60–70°C due to partial protonation of the DMA residues. Under these conditions, MEMA homopolymer remains almost neutral and precipitates at around 40–50°C. Thus, the DMA–MEMA block copolymer was molecularly dissolved in water as a 1.0% solution and the solution pH was adjusted to 7.5 by adding a few drops of HCl. Under these conditions, the DMA block is partially protonated and does not precipitate at elevated temperature, whereas the MEMA block remains essentially unprotonated. Thus, as the solution temperature is increased to 50°C (ie above the cloud-point of the MEMA block), the MEMA block should become hydrophobic and form micelle cores, while the hydrophilic protonated DMA block will form the solvated corona. In addition, micellization should occur at room temperature by the addition of salt at pH 7.5. Again, the DMA block would be partially protonated and form the solvated corona while the MEMA block will be preferentially 'salted out' and form the micelle cores.

The DLS results are summarized in Table 5. There are two methods to prepare MEMA-core micelles with DMA–MEMA diblock copolymers at pH 7.5: (1) at high temperature and low salt concentration (e.g. <0.2 M Na_2SO_4); (2) at 20°C and high salt concentration (e.g. >0.5 M Na_2SO_4). The micelle diameters of the block copolymers are summarized in Table 5. Variations in copolymer molecular weight and block composition have a relatively small effect on the mean micelle diameter.

The micelles formed at 60–65°C are stable but aggregation occurs within minutes if the temperature is increased by just 2–3°C. However, the micelles formed at room temperature in the presence of high salt concentration are more robust and fairly near-monodisperse. Proton NMR studies support the hypothesis that the MEMA block forms the micelle cores under these conditions. Fig. 10 shows the NMR spectra recorded for a 40:60 DMA–MEMA diblock copolymer at pH 8.5 (Fig. 10a), at pH 7.5 (Fig. 10b) in the absence of salt and in the presence of 0.7 M Na_2SO_4 at pH 7.5 (Fig. 10c). All the peaks due to the DMA residues at pH 8.5 are shifted downfield at pH 7.5 due to partial protonation while the positions of the MEMA peaks remain unchanged, since these residues remain unprotonated at this pH (compare Fig. 10a and b). The peaks from the MEMA residues disappear after the addition of salt, (compare Fig. 10b and c), which indicates that they are no longer hydrated. If the salt is removed via dialysis (or if the solution pH is lowered to 2), the micelles dissociate into unimers and the MEMA signals reappear. This confirms the reversible nature of the aggregation.

The fundamental studies reported herein have already been exploited for the synthesis of novel macromolecular nanostructures such as shell-cross linked micelles [43]. In this case micellar self-assembly occurs first, followed by cross-linking of the micelle corona. This is achieved by quaternization: 1,2-bis-(2-iodoethoxy)ethane reacts selectively

Table 5
A summary of the hydrodynamic diameters, PD and solution conditions for a 1.0 w/v% DMA–MEMA diblock copolymer solution at pH 7.5

Sample code	DMA content[a] (mol%)	M_n (g mol^{-1})[b]	Na_2SO_4 conc. (M)	Temp. (°C)	Micelle diameter (nm)[c]	PD[c]
VB41	65	19 200	no salt	24	unimer	–
VB41	65	19 200	0.7	24	19	0.058
VB33A	48	21 550	<0.2	24	unimer	–
VB33A	48	21 550	0.2	51	20	0.042
VB33A	48	21 550	0.7	24	20	0.073
VB37A	38	33 000	no salt	24	unimer	–
VB37A	38	33 000	no salt	65	26	0.188
VB37A	38	33 000	0.7	24	22	0.054
VB190	40	27 600	no salt	65	22	0.304

[a] As determined by ^1H NMR spectroscopy.

[b] As determined by GPC.

[c] As determined on 1 w/v% copolymer solutions by DLS.

with DMA residues on adjacent block copolymer chains to 'lock in' the micelle structure. Permanent ultrafine nanoparticles of 20–40 nm are produced, whose hydrophobic MEMA- or DEA-based micelle cores can become hydrophilic on adjusting the solution temperature, salt concentration or solution pH. Recently we have shown how to carry out shell cross-linked micelle syntheses at high solids whilst avoiding the problem of inter-micelle aggregation [44]. Thus these nanocapsules may have potential as controlled-release delivery vehicles for drugs, pesticides, perfumes, dyes and other active compounds.

4. Conclusions

GTP has been used to prepare a series of water-soluble (co)polymers of narrow molecular weight distribution based on tertiary amine methacrylates. A series of DMA–MEMA, DMA–DEA and DMA–DPA diblock copolymers were synthesized, with molecular weights ranging from 1×10^3 to 5×10^4 g mol^{-1} and DMA contents varied systematically from 20 to 80 mol%. To gain a better understanding of the micellization behaviour of these diblock copolymers, a series of DMA, DEA, DPA and MEMA homopolymers

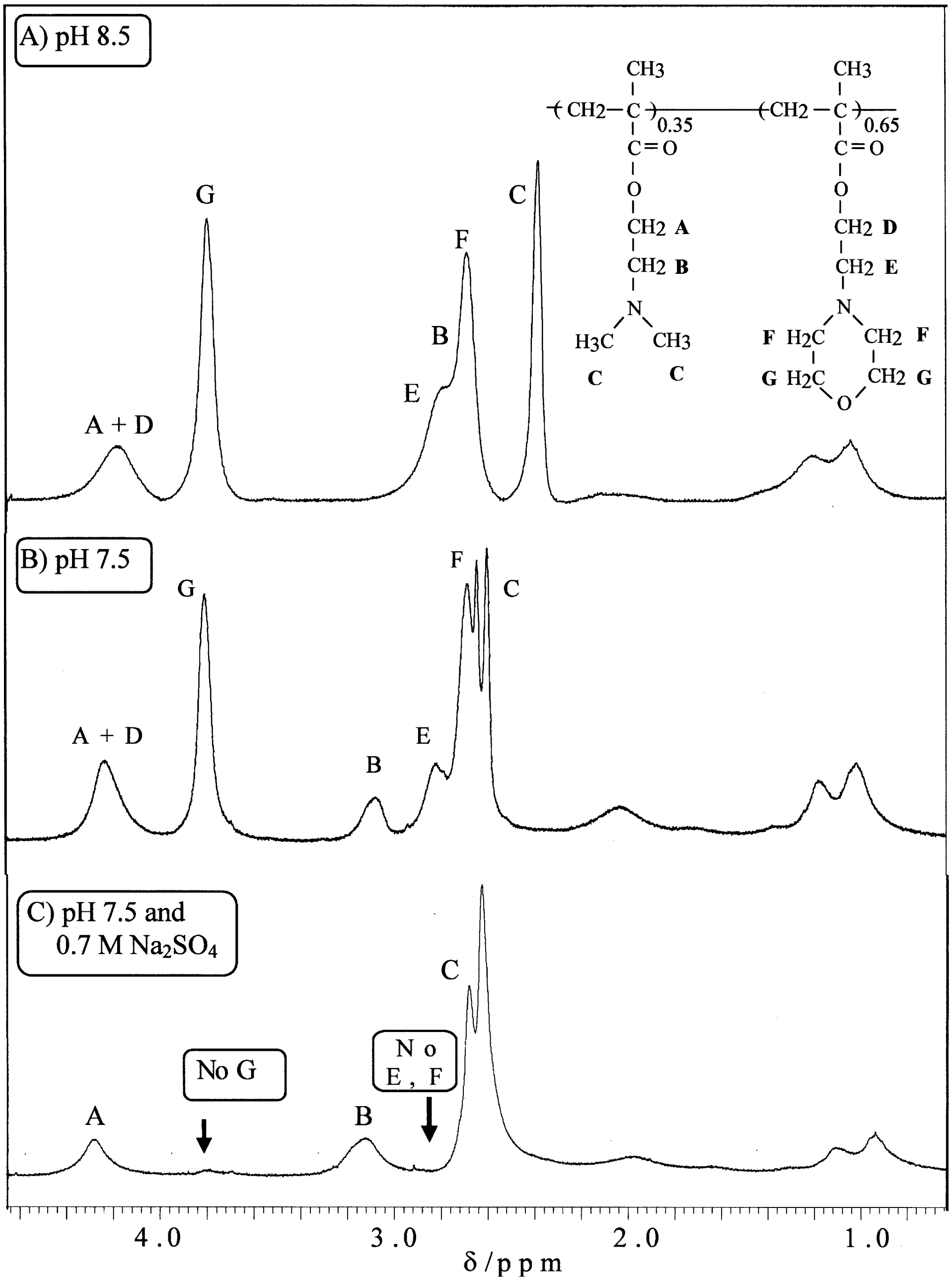

Fig. 10. ^{1}H NMR spectra of a 35:65 DMA–MEMA block copolymer in D_2O at 20°C (M_n = 36 000 g mol^{-1}): (A) at pH 8.3; (B) at pH 7.5; (C) at pH 7.5 in the presence of 0.7 M Na_2SO_4.

were also synthesized. All homopolymers and block copolymers had narrow molecular weight distributions ($M_w/M_n < 1.20$), which is typical for GTP (co)polymers. In some cases, NMR spectroscopy enabled absolute number-average molecular weights to be determined by end-group analysis since the MTS initiator gave a unique NMR signal. The DMA and MEMA homopolymers were water-soluble at neutral pH and exhibited inverse temperature solubility behaviour. The variation of cloud-point with degree of polymerisation was determined for both homopolymers. In contrast, the DEA and DPA homopolymers were water-insoluble at neutral pH but dissolved in acid due to protonation of the amine residues.

Subtle differences in hydrophilicity between the various diblock compositions leads to interesting aqueous solution behaviour including pH-, temperature- and/or salt-induced micellization and high surface activity. Micellization is fully reversible in all cases. pH-induced micellization was observed with both the DMA–DEA and DMA–DPA diblock copolymers. Both salt-induced micellization and temperature-induced micellization were observed with the partially protonated DMA–MEMA diblock copolymers. In all cases the DMA blocks formed the solvated micelle coronas, as shown by NMR studies.

Acknowledgements

VB thanks the University of Osmangazi, Turkey for a PhD studentship.

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