Water soluble polymeric nanogels by xanthate-mediated radical crosslinking copolymerisation

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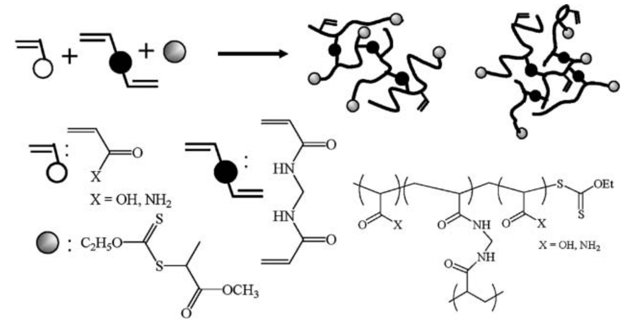
Branched water-soluble copolymers were obtained by direct radical crosslinking copolymerisation of acrylic acid or acrylamide and *N*,*N*′-methylenebisacrylamide at high solid content in the presence of an *O*-ethylxanthate as a reversible chain transfer agent.

"Microgels"[1] sometimes called "polymeric nanogels"[2] are soluble intramolecularly crosslinked polymer chains in the 10–1000 nm size range that can also be viewed as high molar mass "hyperbranched polymers".[1–3] A method generally employed for synthesizing microgels is by radical crosslinking copolymerisation (RCC) of a vinylic monomer with a crosslinker using one of the three following processes: i) highly diluted solution, ii) emulsion and iii) precipitation/dispersion polymerisations.[1,2] Intramolecular crosslinking predominates at the early stages of a regular RCC generating highly heterogeneous microgels whose branching points are irregularly distributed. Recently, Sherrington and colleagues carried out solution RCC of methacrylic-type monomers at relatively high monomer concentrations and succeeded in avoiding macrogelation by employing mercaptans as chain transfer agents (CTA).[3] Attempts at preventing macrogelation and generating polymeric nanogels of better structural homogeneity include the use of "controlled/living" radical polymerisations[4] (C/LRP) techniques such as atom transfer radical polymerisation and nitroxide-mediated polymerisation.[5–8] In a recent addition, Perrier and colleagues took advantage of dithioesters to obtain hydrophobic "hyperbranched" copolymers of polymethacrylate by reversible addition–fragmentation chain transfer polymerisation (RAFT).[9] The synthesis of branched copolymers grown by the same principle were previously reported by two of us in a patent.[10] These few examples show that C/LRP techniques are yet to be fully exploited in RCC for the synthesis of better defined branched copolymers/nanogels.[5–10]

Polymeric nanogels most currently studied by regular RCC are based on pH-sensitive and/or temperature-sensitive hydrophilic polymers, owing to the stimuli-responsive properties in water of these materials. Here we describe the direct synthesis of hydrophilic branched poly(acrylic acid), polyacrylamide and related copolymers obtained by one-pot RCC of acrylic acid or acrylamide in the presence of a *O*-ethylxanthate used as reversible chain transfer agent (RCTA). The use of the xanthate enables the incorporation of large amounts of the crosslinking co-monomer (up to 10 mol%) without macrogel formation and the possibility of generating core-shell star structures by chain extension from the branched copolymeric precursors.

The *O*-ethyl-*S*-1-(methyloxycarbonyl)ethylxanthate (X_A) of structure $C_2H_5O–C(=S)S–CH(CH_3)COOCH_3$, was chosen to mediate the RCC of acrylic acid (AA) and acrylamide (Am) for being known to control the free-radical polymerisation of these monomers in hydroalcoholic solutions by a RAFT-like process,[11] coined MADIX (for MAcromolecular Design by Interchange of Xanthates) by the Rhodia researchers.[12,13] *N*,*N*′-methylenebisacrylamide (MBA) was the crosslinker of choice to react with AA or Am in alcoholic solutions.[1,2] RCCs were thus carried out in ethanol and in a mixture of water and 2-propanol (4/1 v/v) when AA and Am were used as monomers, respectively, in one-pot at 70 °C in the presence of X_A and 4,4′-azobis(4-cyanopentanoic acid) (ACP) as a radical source. Different MBA/AA/X_A and MBA/Am/X_A ratios were investigated to determine both the effect of MBA and X_A during xanthate-mediated RCCs. A sketch of the branched copolymers formed under such conditions is displayed in Scheme 1.

Monomers' and xanthate conversions were determined by gas chromatography (GC), HPLC and ^{1}H NMR spectroscopy. Under the conditions mentioned above, near quantitative yields were obtained after 4 hours at 70 °C, 0.004–0.015% for MBA (by HPLC), 0.13–2.67% for AA (by HPLC), 0.53–1.1% for Am (by ^{1}H NMR) and 0.11–0.15% for X_A (by GC) being the residual amounts respectively found. ^{1}H NMR spectroscopy proved useful as an *in-situ* real time monitoring method of monomers' and xanthate consumption at 70 °C in deuterated ethanol. The ^{1}H



Scheme 1 Synthesis of hydrophilic polymeric nanogels by xanthate-mediated RCC.

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Table 1 Xanthate–mediated RCC of AA (entries 1 to 12) or Am (entries 13 to 22) and MBA at 70 °C[a]

Entry	AA or Am (mol)	MBA (mol)	X_A (mol)	M_n[b] (g mol^{-1})	M_w[b] (g mol^{-1})	PDI
1	98.0	0	2.0	2500	2800	1.15
2	93.0	5.0	2.0	5700	24400	4.27
3	88.0	10.0	2.0	gel	gel	gel
4	95.4	0	4.6	2300	2600	1.16
5	90.5	4.9	4.6	4900	7600	1.53
6	85.5	9.9	4.6	5100	10200	1.99
7	80.6	14.8	4.6	gel	gel	gel
8	93.5	0	6.5	1500	1800	1.19
9	89.0	4.5	6.5	4700	5900	1.25
10	83.7	9.8	6.5	5300	9000	1.71
11	78.8	14.7	6.5	2300[c]	3480[c]	1.51[c]
12	73.8	19.7	6.5	gel	gel	gel
13	84.9	4.0	1.1	7370	42070	5.71
14	92.9	6.0	1.1	gel	gel	gel
15	98.0	0	2.0	1420	2810	1.98
16	96.0	2.0	2.0	1930	5170	2.68
17	93.8	4.1	2.0	3510	13340	3.80
18	92.0	6.0	2.0	4420	52800	11.9
19	90.0	8.0	2.0	gel	gel	gel
20	91.9	4.1	4.0	985	2730	2.77
21	90.0	6.0	4.0	1270	3440	2.72
22	87.9	8.1	4.0	1600	7140	4.42

[a] Copolymerisations of AA/MBA/X_A were carried out in batch in ethanol (20% in weight) using ACP as the radical source (10 mol% relative to X_A); RCC's of Am/MBA/X_A were carried out in a mixture of water/2-propanol (4/1 v/v) at 10% in weight using ACP as the radical source (10 mol% relative to X_A). [b] ASEC calibrated with poly(ethylene oxide) standards. [c] A gel fraction was obtained; ASEC was performed with the soluble part.

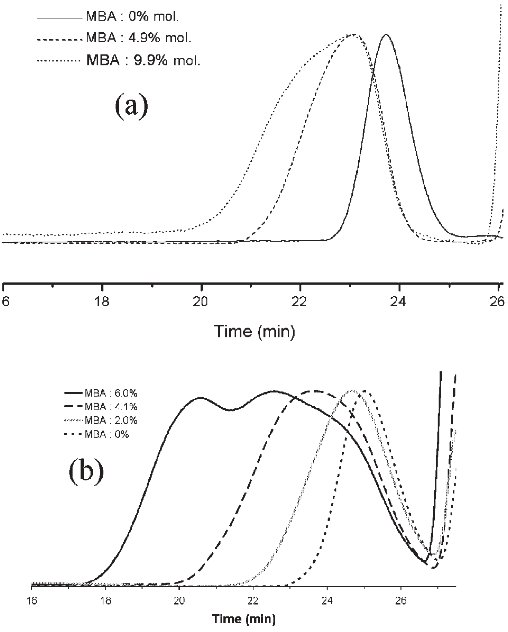


Fig. 1 ASEC traces of the polymeric nanogels obtained by (a) RCC of AA/MBA/X_A (entries 4 to 6, Table 1) and (b) by RCC of Am/MBA/X_A (entries 15 to 18, Table 1).

NMR spectra (D_2O, 400 MHz) of the PAA samples confirmed the presence of the branching MBA moieties. Integration of the peaks attributable to the three reagents allowed one to conclude that MBA, AA and X_A exhibited quasi-identical reactivities in these conditions and that they were thus incorporated at approximately the same rate in the copolymeric chains. The final composition was therefore in good agreement with the molar feed ratio MBA/AA/X_A. Table 1 summarizes the evolution of molar masses and polydispersity indices (PDI's) during xanthate-assisted RCC of AA/MBA and Am/MBA mixtures. Characterisation by aqueous size exclusion chromatography (ASEC) shows an increase of M_w and PDI values with the MBA content for a same X_A concentration (Fig. 1).

While it is highly recommended to perform regular RCC under highly dilute conditions (<5% weight) and discontinue polymerisation before completion in order to obtain polymeric nanogels,[1,2] the use of the MADIX agent X_A permitted high monomer conversion—if not quantitative—at higher solid content as well as a much higher content in crosslinker without occurrence of gelation. Typically, for X_A = 5 mol%, gelation was observed only for a concentration in MBA higher than 10 mol% for a weight concentration of 20% in the case of the RCC of AA/MBA/X_A. In this case, both crosslinker and RCTA have a dramatic effect on the build-up of molar masses of the branched copolymers: i) the higher the concentration of [MBA], the larger the molar masses and polydispersities for a given [X_A] (Fig. 1) and, ii) the lower the [X_A], the larger the molar masses for a fixed [MBA] (Fig. 2). Similar trends were observed for PAm-based polymeric nanogels obtained by RCC of various Am/MBA/X_A mixtures (Table 1, Figs. 1 and 2). In the latter case, the concentration was fixed at a weight concentration of 10% in a mixture of water–2-propanol (4/1 v/v). Higher concentrations generally led to macrogelation.

One major advantage of these xanthate-assisted RCCs is the possibility of growing further chains from dormant ones (Scheme 2). In this way, star-like structures with a polymeric nanogel core are obtained in a divergent fashion. As a proof of concept, Fig. 3 shows the shift to the higher molar masses observed

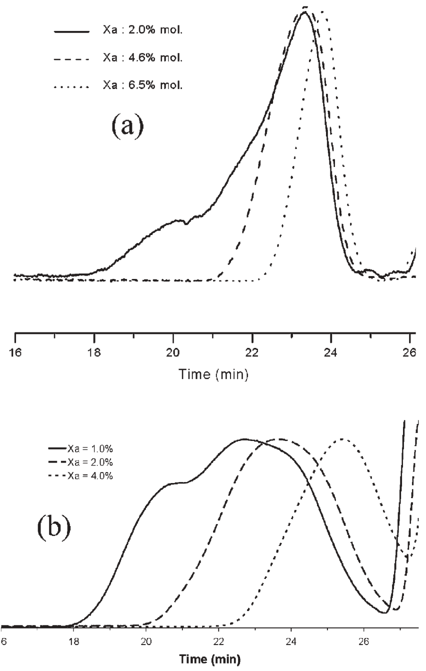
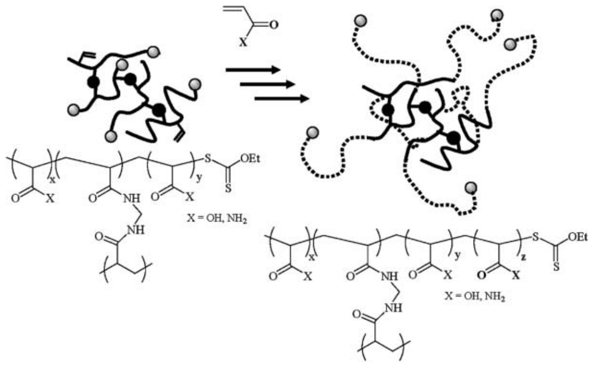


Fig. 2 Effect of xanthate concentration on the ASEC traces of polymeric nanogels obtained (a) by RCC of AA/MBA/X_A (entries 2, 5 and 9, Table 1) and (b) by RCC of Am/MBA/X_A (entries 13, 17 and 20, Table 1).



Scheme 2 Synthesis of a star-like structure by chain extension of a polymeric nanogel obtained by xanthate-mediated RCC.

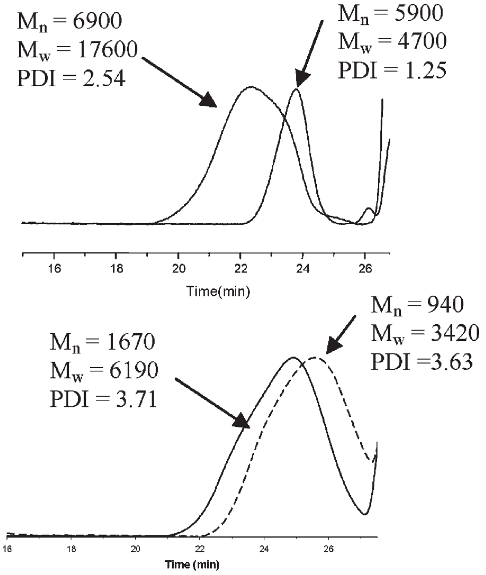


Fig. 3 ASEC traces of polymeric nanogel: (a) entry 9, Table 1; (b) entry 21, Table 1 and star-like copolymer after extension polymerisation of AA (a) or Am (b).

in the ASEC traces, after direct chain extension with AA and Am from a poly(acrylic acid)-based and a polyacrylamide-based copolymer, of initial composition MBA/AA/X$_A$ = 4.5/89/6.5 (entry 9, Table 1) and MBA/Am/X$_A$ = 6.0/90/4.0 (entry 21, Table 1), respectively. These parent nanogels served as a macromolecular multifunctional RCTA for the MADIX polymerisation of AA and Am in pure water, following a core-first approach using ACP. Near quantitative yields were obtained after 7 hours of polymerisation with no visible formation of macrogel. This supports the advantage of polymerising highly reactive monomers *via* this core-first methodology. Indeed, synthesis of core-first stars by RAFT is sometimes complicated by irreversible terminations between stars, especially for poorly reactive radicals such as polystyryl ones.[14] With more reactive radicals, however, like those here deriving from PAA or PAm, the probability for stars becoming coupled is minimized, owing to higher k_p^2/k_t ratio as compared to styrene, k_p and k_t being the rate constant of propagation and the rate constant of termination, respectively.

In summary, water-soluble polymeric nanogels,[15] that can be viewed as both highly and yet evenly branched copolymers, could be obtained by one-pot RCC of acrylic acid or acrylamide and *N*,*N*′-methylenebisacrylamide—with no need to protect the functional group of these monomers—in the presence of a *O*-ethylxanthate as a reversible chain transfer agent used to avoid macrogelation. The molar masses and polydispersities of these branched copolymers could be varied at will as a function of the concentrations of the starting reagents. Even in the presence of a rather high proportion of crosslinker, no macrogelation was observed provided enough xanthate was utilized. Chain extension from these nanogels afforded multi-arm star polymers and a practical pathway to this kind of architecture. Investigations are in progress to determine how evenly distributed are the branching points within these polymeric nanogels, xanthate-mediated RCC being expected to afford more uniform branched copolymers than those obtained under regular RCC conditions.

The authors are grateful to Rhodia for permission to publish this work.

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15 As suggested by one referee, the size of compounds prepared by RCC of AA(or Am)/MBA/X$_A$ was determined by dynamic light scattering using the Zetasizer (Malvern) in aqueous solutions at a concentration of 0.1%, at pH = 4.5 for PAA samples. The hydrodynamic diameter (D_H) could be calculated from the diffusion coefficient using the Stokes–Einstein relation. In the series investigated in this work, the D_H values were in the range 14–93 nm. Thus, these systems do enter in the category of "polymeric nanogels", as defined in the introduction. A detailed study of the solution properties of these polymeric nanogels will be described in future publications.