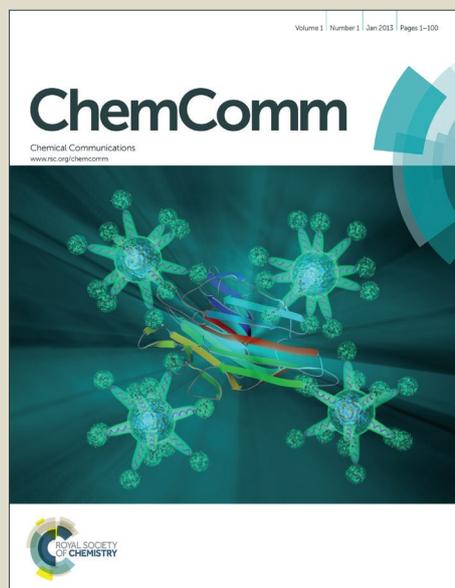


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COMMUNICATION

A triple carboxylic acid-functionalized RAFT agent platform for the elaboration of well-defined telechelic 3-arm star PDMAc

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This communication describes the synthesis of a three acid-functionalized RAFT agent and its use to prepare well-defined 3-arm star polymers of *N,N*-dimethylacrylamide (DMAc). A simple esterification reaction allowed the convenient integration of three electron-rich naphthalene recognition units on the RAFT agent platform and subsequently the elaboration a naphthalene end-decorated telechelic 3-arm star PDMAc. This functionalized star polymer was further exploited to build a hydrogel with a complementary homoditopic host unit featuring tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) units.

Among contemporary controlled radical polymerization (CRP) techniques, reversible addition-fragmentation chain transfer (RAFT) polymerization is notable as it facilitates the preparation of polymeric materials with well-controlled molar masses and well-defined architectures from a wide variety of monomers at convenient temperatures using a variety of solvents.¹ In 2003, Mayadunne *et al.*² demonstrated the potential of thiocarbonyl thio derivatives to conveniently build star polymers. Since then, due to their potential applications in a number of areas (e.g. biomedical,³ cosmetics⁴), multi-armed star polymeric architectures have been intensively studied.^{1,5} There are two main methods for the creation of polymer stars, which either involves construction of the arm first or the core first. The arm first approach involves the synthesis of pre-formed polymeric arms which are then coupled together. The core first strategy exploits a multifunctional initiator as the central core from which polymer chains are grown from the initiating sites. The number of arms per star is controlled by the number of initiation sites per core. In this context, all multifunctional (with a number of end-caps ≥ 3) RAFT agents

previously employed using Z-group approach were end-capped with hydrophobic (mainly phenyl, benzyl or alkyl groups) and non-reactive groups (except the thiocarbonyl thio moiety). The star polymers prepared via RAFT process using R-group approach are also mainly end-capped with the same kind of hydrophobic groups.

Hence, it is of interest to develop other kinds of RAFT agents capable of conveniently giving rise to telechelic star polymers that can be further modified and/or exploited to create materials of interest. In the present study, we describe the synthesis of the first triple acid-functionalized RAFT agent **1** (containing three trithiocarbonates having a functional Z group) allowing to access to telechelic star polymers by a divergent approach (R-group approach). While mono and bifunctional carboxylic acid-functionalized RAFT agents^{1,6} have already been described and are ubiquitous in the literature for the synthesis of functional RAFT agents, analogous trifunctional RAFT agents have not been reported to the best of our knowledge. The incorporation of carboxylic acid groups into RAFT agents is particularly attractive as they allow post-modification using facile coupling chemistry, thereby affording functionalized multi-arm systems after RAFT polymerization. Furthermore, multifunctional star polymers with functionality > 2 are of interest owing to their propensity of creating cross-linked materials such as hydrogels.⁷ Furthermore, as a proof of concept, we also report the synthesis of a functionalized RAFT agent featuring three electron-rich naphthalene guest units, prepared from **1** by esterification reactions, and its use to produce a trifunctional telechelic 3-arm star polymer of *N,N*-dimethylacrylamide (PDMAc). Interestingly, preliminary physical experiments (inverted vial tests) revealed the facility of the naphthalene based telechelic 3-arm star PDMAc to afford a coloured supramolecular hydrogel in the presence of a complementary electron-deficient homoditopic tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) host molecule.

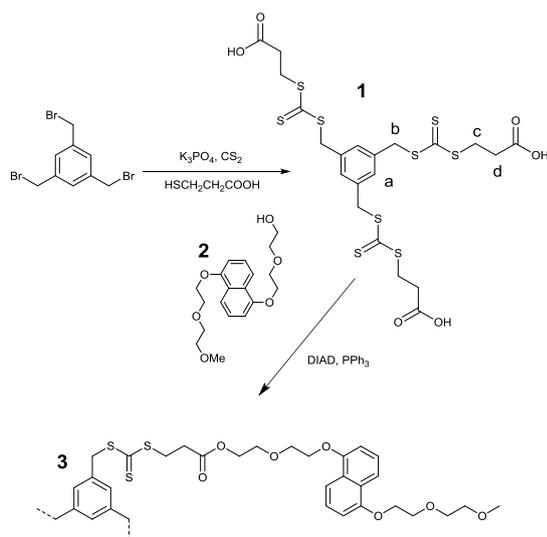
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Scheme 1 Strategy for the synthesis of new trifunctional RAFT agents.

To synthesize the new reversible chain transfer agent **1**, we employed the universal and mild synthetic procedure for the high yielding synthesis of a diverse range of RAFT agents reported by O'Reilly *et al.*⁸ (Scheme 1). By using these conditions, the trifunctional trithiocarbonate **1** can be conveniently obtained in good yield (63%), in less than 3h and without purification by column chromatography being required (see ESI[†]). ¹H NMR spectrum of tricarboxylic acid-CTA recorded in acetone-*d*₆ displays the characteristic signals of the Z-group ((3-propionic acid)sulfanyl moiety) unit in addition to those belonging to the core (R-group: 1,3,5-(trimethylene)benzene moiety) (Fig. 1). The ¹³C spectrum (Fig. S1, ESI[†]) clearly also shows chemical shifts near 173 ppm and 224 ppm originating from the carbonyl of the acid group and the thiocarbonyl fragment of the trithiocarbonate CTA, respectively.

Having prepared **1**, its effectiveness as RAFT agent in the RAFT polymerization of DMAc was evaluated by using the conditions reported by Laschewsky *et al.*^{5d} for the synthesis of amphiphilic star polymers (*i.e.* at an elevated temperature (90°C) to favour fast propagation and in benzene to avoid radical chain transfer to the solvent). 1,1'-Azobis(cyclohexanecarbonitrile) (ACHN) was used as initiator in order to maintain a sufficiently low formation of primary radicals during the polymerization process. As depicted in Table 1, the polymerization (**P**₁) under these conditions proceeded rapidly and high monomer conversion (85%) was reached after only 1.5h. Moreover, RAFT polymerization exhibited pseudo-first order kinetics (Fig. S5, ESI[†]) with a very low induction period (about 6 min). RAFT homopolymerization was controlled as the growing polymer exhibited a linear increase of *M*_n with monomer conversion and dispersity (*D*) below 1.4 (**P**₁, Table 1). Throughout the polymerization, SEC traces were essentially symmetrical and narrow in shape (Fig. S6, ESI[†]). Thereby, under these conditions, we were able to prepare a carboxylic acid end-capped 3-arm star polymer made of the hydrophilic monomer

(DMAc) (structure given in Fig. S9, ESI[†]) by RAFT polymerization in high yield with a molar mass of about 111 kg mol⁻¹ and with a quite narrow molar mass distribution (*D* = 1.4). The estimated end group number was close to 3, as determined by ¹H NMR (see Fig. S7). When the monomer to RAFT molar ratio was multiplied by about 2 ([DMAc]₀ / [**1**]₀ = 2092 for **P**_{1bis}, Table 1), good control of the polymerization of DMAc was still observed up to 80% of conversion and a high molecular weight star polymer **P**_{1bis} (167.1 kg mol⁻¹) with a relatively low dispersity of 1.38 was isolated.

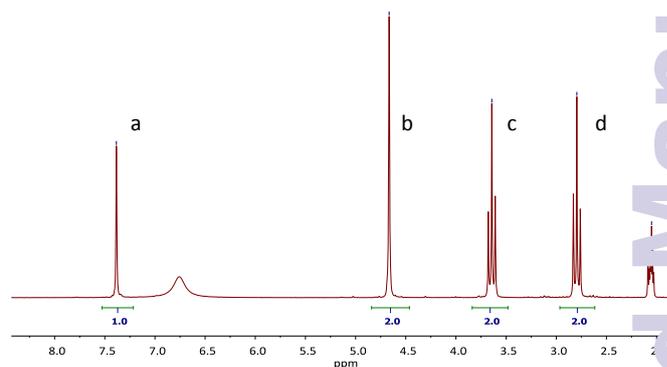


Fig. 1 ¹H NMR spectrum of the tri(carboxylic acid)-functionalized RAFT agent **1** recorded in acetone-*d*₆ at 25°C.

Table 1. Macromolecular characteristics of the star polymers prepared via RAFT polymerization of DMAc in the presence of the trifunctional RAFT agents (**1** and **3**) and 1,1'-azobis(cyclohexanecarbonitrile) (ACHN) as an initiator in benzene at 90°C.

Exp.	Time (min)	conv. ^{a)} (%)	<i>M</i> _{n,th} ^{b)} (kg mol ⁻¹)	<i>M</i> _{n,exp} ^{c)} (kg mol ⁻¹)	<i>M</i> _n ^{LS,d)} (kg mol ⁻¹)	<i>D</i> ^{e)}
P ₁ ^{e)}	10	9.6	11.3	-	-	-
	30	43.9	45.8	21.1	61.6	1.18
	45	57.1	59.1	32.2	75.3	1.38
	90	85.3	87.4	48.8	105.2	1.38
P _{1bis} ^{f)}	15	18.1	38.2	7.7	44.2	1.52
	32	58.6	122.2	59.7	136.1	1.27
	47	80.3	167.1	76.7	191.1	1.38
P ₂ ^{g)}	15	5.8	13.7	20.7	34.1	1.26
	32	42.6	89.9	64.2	77.7	1.11
	47	57.1	120.0	80.8	131.6	1.24
	77	77.3	161.8	105.2	172.8	1.15

a) Monomer conversion determined by ¹H NMR. b) Theoretical number-average molar mass at the experimentally determined conversion. c) Number-average molar mass, *M*_n and dispersity, *D* determined by SEC in DMF (+ LiBr) using PMMA standards. d) The number-average molar mass based on static light scattering detection, *M*_n^{LS}, were determined using the experimental *dn/dc* values (0.066 mL g⁻¹ for **P**₁ and **P**_{1bis} and 0.073 mL g⁻¹ for **P**₂, see Fig. S14, ESI[†]). e) In the presence of **1**, [ACHN]₀ / [**1**]₀ = 0.2 and [DMAc]₀ / [**1**]₀ = 1070. f) In the presence of **1**, [ACHN]₀ / [**1**]₀ = 0.4 and [DMAc]₀ / [**1**]₀ = 2092. g) In the presence of **3**, [ACHN]₀ / [**3**]₀ = 0.4 and [DMAc]₀ / [**3**]₀ = 2090.

Having demonstrated the faculty of **1** to control the polymerization of DMAc, we next turned our attention to whether the functionalized RAFT agent **3** (Scheme 1) featuring three dialkyloxynaphthalene units could also be used to elaborate a naphthalene end-decorated telechelic 3-arm

PDMAc. Integrating such electron-rich recognition units into polymer scaffold is indeed particularly attractive as they have been demonstrated to be capable of forming host-guest complexes with tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) host⁹ components, thereby allowing the structure and properties of the polymer to be tuned through molecular recognition^{10,11}. Here, we have exploited the presence of naphthalene units onto a star-like polymer architecture to produce a supramolecular hydrogel with a complementary homoditopic cyclobis(paraquat-*p*-phenylene) host molecule **6** (see Fig. 4 and Scheme S1, ESI[†]).

The new RAFT **3** agent bearing three dialkyloxynaphthalene units was conveniently synthesized by Mitsunobu reaction of three equivalents of 1-[2-(2-hydroxyethoxy)ethoxy]-5-[2-(2-methoxy-ethoxy)ethoxy]-naphthalene **2** with the three carboxylic acid-functionalized RAFT agent **1** (Scheme 1). The analytical data for **3** were consistent with the proposed structure (see Fig. 2, Fig. S2 and S16, ESI[†]).

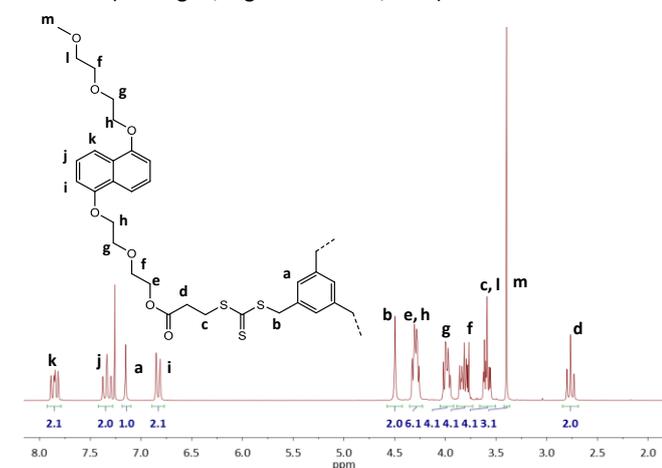


Fig. 2 ¹H NMR spectrum of the tri(dialkyloxynaphthalene)-functionalized RAFT agent **3** recorded in CDCl₃.

Under the polymerization conditions previously used, we were able to prepare a 1,5-dialkyloxynaphthalene end-capped 3-arm star polymer (PDMAc) (structure given in Fig. S9, ESI). The polymerization **P**₂ (Table 1) was also well-controlled as the growing recovered polymers exhibited a linear increase of *M*_n with monomer conversion and the values were in quite good agreement with the theoretical ones, indicating a good efficiency of the trifunctional RAFT agent (see Figures S10-12 and S15, ESI[†]). The estimation of end group functionality was also close to 3 as determined by ¹H NMR (see Fig. S13). The efficiency of the transfer reaction during the formation of star polymer was further confirmed by using SEC equipped with an in-line UV detector. Indeed, the SEC trace recorded at 309 nm (a wavelength where the trithiocarbonate functionality strongly absorbs),^{5d} revealed a fairly symmetric number distribution, showing no significant tailing toward the higher molar mass side, thereby indicating that the final polymer was almost free of star–star coupling and that the formed star polymer was terminated by trithiocarbonate units. The formed star polymer could be thus be utilized as macromolecular chain transfer agent in a subsequent polymerization reaction to form a A₃B₃-type macromolecular structure.

Next, we have investigated the binding properties of **P**₂ (*M*_n = 165 kg mol⁻¹, determined by ¹H NMR, see Fig. S13, the absolute *M*_n value determined by SEC was 173 kg mol⁻¹ and *D*_w = 1.26) towards cyclobis(paraquat-*p*-phenylene) (CBPQT⁴⁺, **6**) (7 in Fig. 4). The ability of star polymer **P**₂ to form supramolecular host-guest complexes with monomeric CBPQT⁴⁺, 4Cl⁻ in water was first evaluated by isothermal titration calorimetry, which revealed a large association constant (*K*_a) of 1.39 (± 0.07) × 10⁵ M⁻¹ and a binding stoichiometry, *N*, of around 3 (Fig. 3) Furthermore, a UV-Vis titration, based on monitoring of the intensity of the characteristic charge-transfer absorption band (centered around 525 nm)¹² of complex **P**₂:CBPQT⁴⁺, 4Cl⁻ following the addition of aliquots of CBPQT⁴⁺, 4Cl⁻ to a solution of **P**₂ in water, confirmed the binding stoichiometry of 3 (see Fig. S17, ESI[†]). These results clearly demonstrate that all of the dialkyloxynaphthalene moieties located on star polymer **P**₂ are available and easily accessible for complex formation with CBPQT⁴⁺.

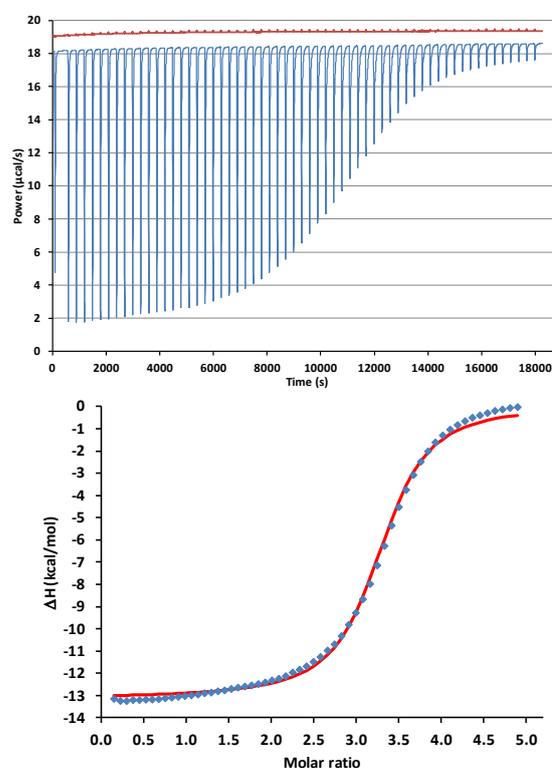


Fig. 3 Isothermal titration calorimetry data for the addition of aliquots of CBPQT⁴⁺, 4Cl⁻ to **P**₂ (0.30 mM). Recorded in H₂O at 20 °C (*K*_a = 1.39 (± 0.07) × 10⁵ M⁻¹, *N* = 3.28).

Finally, **P**₂ and the homoditopic tetracationic macrocycle cyclobis(paraquat-*p*-phenylene) **6** (Fig. 4) were mixed together in equimolar quantity of naphthalene and CBPQT⁴⁺ groups in H₂O resulting in the immediate appearance of a purple color similar to that observed with monomeric CBPQT⁴⁺. However, in this case the ditopic unit **6** facilitated the formation of a hydrogel as indicated by the formation of a viscous gel-like substance during inverted vial tests (Fig. 4). When **P**₂ and

CBPQT⁴⁺, 4Cl⁻ were mixed together, no visible gelation occurred, thus suggesting that hydrogel formation originated from the creation of a cross-linked array between **P**₂ and **6**.

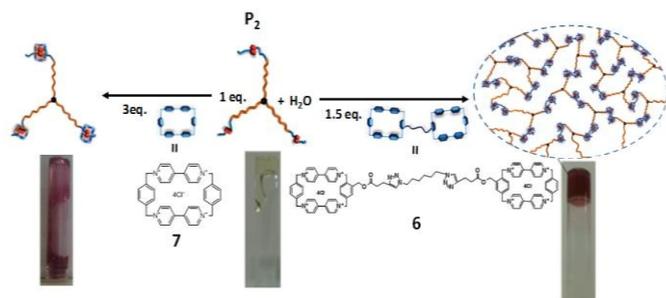


Fig. 4 Schematic representation of the supramolecular polymer network formation via host-guest complexation between 1,5-dialkyloxynaphthalene (**7**) and CBPQT⁴⁺ (**6**) moieties and photographs of the inverted aqueous solutions of **P**₂ and CBPQT⁴⁺, 4Cl⁻ (25 wt%, molar ratio: 1:3) (left), of **P**₂ (25 wt%) (middle) and of a mixture of **P**₂ and **6** (25 wt%, molar ratio: 2:3) (right) at 25°C (after 5 s).

Conclusions

In this communication, we have described a straightforward approach allowing the easy preparation of tricarboxylic acid telechelic 3-arm star polymers using the “core first” methodology from a triple carboxylic acid-RAFT agent. Using a simple esterification reaction, this agent was then conveniently further modified to form a RAFT agent incorporating three electron-rich 1,5-dialkyloxynaphthalene units. This functionalized RAFT agent was also found to be able to control the polymerization of DMAc, leading to the formation of a well-defined end-decorated 1,5-dialkyloxynaphthalene star polymer. The latter was then exploited to elaborate a supramolecular hydrogel in the presence of a complementary homoditopic host unit. Rheological properties of the new hydrogels are under active investigation. Our current work is directed towards the reversible physical properties of the network and this will be reported in due course.

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