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Synthesis, binding and self-assembly properties of a well-defined pillar[5]arene end functionalised polydimethylacrylamide
Synthesis, binding and self-assembly properties of a well-defined pillar[5]arene end functionalised polydimethylacrylamide

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The synthesis, binding and self-assembly properties of a well-defined pillar[5]arene end-functionalised poly(dimethylacrylamide)(MePilla-PDMAC) are reported. In order to synthesise MePilla-PDMAC, a new trithiocarbonate type RAFT agent MePilla-CTA was developed incorporating a partially methylated pillar[5]-arene moiety. Kinetic studies clearly indicated the propensity of MePilla-CTA to control the polymerisation of DMAC. Interestingly, as PDMAC type chains display good solubility both in organic and aqueous media, MePilla-PDMAC was able of specifically bind electron deficient guest molecules at the α-chain-end both in chloroform and water. Complex formation was found to be reversible upon addition of chloride anions or heating in organic and aqueous media, respectively. Furthermore, cryo-TEM, VT-NMR (1H) and VT-DLS investigations also indicated the ability of MePilla-PDMAC to self-assemble into micelle-like aggregates in water showing reversible recognition properties.

Introduction

The amalgamation of polymer and supramolecular chemistry has led to the development of fascinating self-assembling polymeric materials with bespoke structures and tuneable properties.1,2 The incorporation of non-covalent recognition motifs into polymeric systems offers the unique opportunity to tune polymer structures (e.g., topology and morphology) and impart unique additional properties, including self-healing,3 adaptability4 and responsiveness5–7 to materials. Furthermore, the non-covalent modification of polymers has allowed their solubility and correspondingly their processability to be greatly improved.8 The development of this field has largely gone hand-in-hand with the enormous progress that has been made in the development of well-defined polymers synthesised using controlled radical polymerisation (CRP) techniques that feature specific recognition motifs (hydrogen acceptor/donor,10,11 ionic unit,12,13 metal/ligand,14,15 host/guest16–18 molecules) attached in specific locations (end or side chain) to polymer backbones.

Pillar[n]arenes (n = 5, 6, 7, 8...) have emerged as important host units for the construction of supramolecular assemblies with applications spanning materials,19,20 medicine21–23 and sensing.24,25 Their burgeoning interest as macrocyclic hosts relies mainly on their convenient synthesis,26 ability to be conveniently functionalised and their unique symmetrical and rigid electron-rich pillar architecture that enable various neutral and electron-deficient guests to be accommodated within their cavities.27–30 Due to the hydrophobic nature of these macrocycles, host–guest complexation and self-assembly of pillar[n]arene derivatives has been largely investigated in organic media. However, as many recognition events in nature occur in aqueous media, effort has also been directed towards the development of pillarene based receptors capable of recognizing guests in aqueous environments. In this context, the main strategy consists of grafting hydrophilic groups, such as carboxylate,31–33 ammonium,34,35 phosphoniu,36 glycol37 and carbohydrate38 substituents onto the macrocycle.

Despite the advantages of CRP techniques including their flexibility, tolerance to a wide range of monomers, well-defined compositions, narrow molar mass distributions and sophisticated architectures, surprisingly few pillarene-based examples have been reported in the literature. In this context, the RAFT (Reversible Addition–Fragmentation Chain Transfer) has been very recently used to develop thermoresponsive pil-
lararene-containing polymers capable of stabilizing gold nanoparticles\(^{39}\) and creating gel-like supramolecular networks\(^{40}\).

Here, we describe the synthesis of a trithiocarbonate-type RAFT agent **MePilla-CTA** incorporating a partially methylated pillar[5]arene moiety and its propensity to control the polymerisation of DMAC (Dimethylacrylamide) and, therefore, to produce a well-defined methylated pillar[5]arene end functionalised polydimethylacrylamide (PDMAC) (**MePilla-PDMAC**) (Scheme 1). An interesting characteristic of the PDMAC type chain is that it imparts solubility in both aqueous and organic solvents to the methylatedpillar[5]arene scaffold. This feature was exploited to specifically and reversibly end-modify **MePilla-PDMAC** (\(M_n,\text{NMR} = 14,500\) g mol\(^{-1}\), \(D = 1.1\)) with electron deficient partners (G1 and G2) through host-guest complexation both in organic and aqueous media. Preliminary self-assembly properties of **MePilla-PDMAC** in water are also described.

### Results and discussion

The RAFT agent **MePilla-CTA** was conveniently prepared by coupling the N-hydroxysuccinimide (NHS) activated ester of the trithiocarbonate 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionic acid (CTA-NHS)\(^{41}\) and the mono amino pillararene derivative **MePilla-NH\(_2\)**\(^{42}\) (Scheme 2). The analytical data for **MePilla-CTA** were consistent with the proposed structure. The \(^1\)H NMR spectrum of **MePilla-CTA** recorded in CDCl\(_3\) at 298 K shows the characteristic signals of the pillararene unit in addition to those belonging to the isobutylsulfanylthiocarbonylsulfanyl \([\text{CH}_3\text{CH–CH}_2\text{S–C(S)–S–}]\) moiety (Fig. 1). The \(^{13}\)C NMR spectrum (Fig. S1†) also confirmed the identity of **MePilla-CTA** through the appearance of chemical shifts near 173 and 220 ppm ascribed to the carbonyl of the amide group and the thiocarbonyl moiety, respectively.

Having the **MePilla-CTA** in hand, we next investigated its ability to control the polymerisation of DMAC via a RAFT procedure. RAFT polymerisation of DMAC was carried out by using 2,2’-azobis(2-methylpropionitrile) (AIBN) as initiator at 343 K in DMF in the presence of **MePilla-CTA** ([DMAC]\(_0\)/[CTA]\(_0\)/[AIBN]\(_0\) = 1000/5/1). As shown in Fig. 2a, the RAFT polymerisation exhibits pseudo-first order kinetics indicating a constant propagating radical concentration during the polymerisation.

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### Scheme 1

Chemical structures of **MePilla-CTA**, **MePilla-PDMAC**, G1 and G2.

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### Scheme 2

Synthesis of **MePilla-CTA**.

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### Fig. 1

\(^1\)H NMR spectrum of **MePilla-CTA** (300 MHz, CDCl\(_3\)).

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### Fig. 2

(a) First-order kinetic plot for the RAFT polymerisation of DMAC using **MePilla-CTA**; (b) dependence of the number-average molar mass (\(M_n\)) and dispersity (\(D\)) on conversion, for the RAFT polymerisation of DMAC in DMF using **MePilla-CTA**.
Control over molecular weight was also demonstrated by
the linear increase of $M_n$ versus DMAC conversion and disper-
sity ($D$) values of the resulting polymers of 1.1–1.3 (Fig. 2b).
SEC analysis also revealed polymers with symmetrical traces
(Fig. S4†) and experimental molar masses in accordance with
theoretical values, indicating that the number of chains is gov-
erned by the RAFT agent concentration which remained con-
stant during the polymerisation. The pseudo-living character of
the RAFT polymerisation was also evidenced by restarting the
polymerisation of DMAC from a macromolecular RAFT agent
($M_{n,SEC} = 22260$ g mol$^{-1}$) which gave rise to a well-defined
polymer with a higher molar mass ($M_{n,SEC} = 59500$ g mol$^{-1}$)
with a narrow molecular mass distribution ($D = 1.3$) (Fig. S5†).

The $^1$H NMR spectrum recorded in CDCl$_3$ of MePilla-
PDMAC (Fig. 3) clearly shows the presence of the pillarene
unit connected to polymer chains with the presence of charac-
teristic resonances of $H_{1,2}$ ($\delta = 6.7$ ppm) and $H_3$ ($\delta = 3.7$ ppm)
belonging to the host unit and PDMAC chains ($0.8 < \delta < 3.2$ ppm).
This was further confirmed by performing 2D diffusion-ordered spectroscopy (DOSY) $^1$H NMR experiments
that showed a single diffusion coefficient value of $0.6 \times 10^{-10}
$ m$^2$ s$^{-1}$ at 298 K for the aforementioned protons in CDCl$_3$.

An interesting characteristic of the PDMAC type chain is
that it imparts solubility in water and organic solvents to the
methylatedpillar[5]arene scaffold, thereby allowing binding
properties of MePilla-PDMAC to be investigated in both aqueous
and organic media. The complexation properties of MePilla-
PDMAC were first investigated by $^1$H NMR spectroscopy in
CDCl$_3$ and D$_2$O (Fig. S6†) in the presence of G1 and
G2 as guest molecules, respectively. In both cases, a broaden-
ing and a shielding effect for the resonances of protons of the
guest and host partners were observed. This is particularly
noteworthy for $H_{a,1}$, $H_{b,1}$, and $H_{c,1}$ of G1 that show upfield shifts
of 0.3, 2.2, and 3.6 ppm upon complexation in CDCl$_3$, respectively.
A slight downfield shift ($+0.05$ ppm) was also observed for
$H_{1,2}$ protons of MePilla-PDMAC. A similar trend was evidenced for
$H_{c,2}$ and $H_{d,2}$ of G2 that shift upfield by 0.3 and 3.2 ppm in
D$_2$O, respectively, upon the addition of an equimolar solution
of MePilla-PDMAC (Fig. S6†).

To further prove the ability of MePilla-PDMAC to form
pseudorotaxane-like complexes with G1 and G2, 2D-NOESY
(Fig. S7†) and 2D-DOSY (Fig. 4B) experiments were under-
taken. As expected, correlations between most aromatic and
alkyl protons of guest molecules G1/G2 and protons located
on the host unit were observed, suggesting the formation of
pseudorotaxane architectures between MePilla-PDMAC and G1
and G2. 2D-DOSY experiments showed that $H_{1,2}$ protons
of MePilla-PDMAC were not impacted in terms of diffusion coefficient by the presence of the significantly smaller guest mole-
cules G1 and G2. On contrary, the diffusion coefficient values of $H_{a,1}$ and $H_{c,2}$ of G1 and G2, respectively, were dramatically
affected upon complexation and moved to much lower and
almost identical values to those obtained for MePilla-PDMAC
in the different media, thereby further demonstrating the for-
mation of complexes. Finally, association constants for
MePilla-PDMAC complexing with G1 and G2 were estimated by
$^1$H NMR (in CDCl$_3$) and fluorescence (in H$_2$O) titration experi-

\[ \text{Fig. 3} \quad ^1\text{H NMR spectrum of MePilla-PDMAC ($M_n = 14500$ g mol$^{-1}$)} \]
recorded in CDCl$_3$ at 298 K.
ments and were found to be 0.9 (±0.1) × 10^2 (Fig. S8†) and 1.5 (±0.1) × 10^3 M⁻¹ (Fig. S9†), respectively, by employing a non-linear fitting method using one-site binding models. In addition, the 1:1 binding mode was further evidenced through the continuous variation method (Job plot method) using ¹H NMR spectroscopy (Fig. S10†).

With complexation confirmed for MePilla-PDMAC-G1 and MePilla-PDMAC-G2 in chloroform and water, respectively, we next turned our attention to whether complex formation of this type could be controlled by applying an external stimulus. First, we investigated the opportunity to switch off the complexation between MePilla-PDMAC and G1 in chloroform by adding chloride anions. Indeed, Huang43 and Wang24 have recently demonstrated that pillararene based complexes could be dissociated in chloroform by adding tetrabutylammonium chloride (TBACl), leading to the exchange of the soft counter ion PF₆⁻ of the guests by a hard counter ion Cl⁻ and the formation of an intimate ion pair between ammonium cations and Cl⁻.

Fig. 5A shows the evolution of chemical shifts corresponding to the MePilla-PDMAC-G1 complex in the presence of an excess of TBACl. As expected, a disassembly process between G1 and MePilla-PDMAC can be observed through a downfield and upfield shift of Ha-1 and H1,2 protons, respectively, that move toward the resonances observed for the uncomplexed G1 and MePilla-PDMAC.

Next, we have explored the effect of heating the MePilla-PDMAC-G2 complex using variable-temperature ¹H NMR (Fig. 5B) and 2D-DOSY experiments (Fig. S11†). As shown in Fig. 5B, a clear gradual downfield shift in the resonances of Hₐ-2, Hₚ₂, Hₜ₂ of G2 with a concomitant sharpening of NMR signals for both guest and host moieties was observed. This is particularly noticeable for Hₐ-2 and Hₚ₂ which split into two distinct and sharp signals at 340 K, which is similar to the resonances observed in the NMR spectrum of the uncomplexed G2. Moreover, a similar behaviour was evidenced by estimating diffusion coefficients for Hₚ₂ and Hₜ₂ versus temperature. Indeed, while D(Hₚ₂) remained almost identical with temperature, D(Hₜ₂) increased progressively from 300 to 340 K and then rose sharply above this temperature, thereby suggesting a disassembly of the complex (Fig. S11†). To confirm this dissociation with temperature, VT-fluorescence studies were carried out on the uncomplexed MePilla-PDMAC and the MePilla-PDMAC-G2 complex. While the complexed MePilla-PDMAC shows a much lower relative fluorescence intensity than the free MePilla-PDMAC at 300 K, above 340 K both species display a nearly identical relative fluorescence intensity to their non-complexed states, thereby suggesting the dissociation of the MePilla-PDMAC-G2 upon heating (Fig. S12†).

Having demonstrated that the methylatedpillararene moiety was located at one end of PDMAC chain, and that specific non-covalent modification with electron deficient guests was possible, we next investigated the impact of the presence of the hydrophobic pillararene unit on PDMAC chains and host–guest complexation has on the self-assembly properties of MePilla-PDMAC in water. DLS (Fig. 6A) and cryo-
TEM (Fig. 6B) experiments were carried out on MePilla-PDMAC which revealed the existence of nanosized aggregates with an average hydrodynamic diameter ($<D_h>$) of 24 nm (poly: 0.02) corresponding to micelle-like aggregates (according to the cryo-TEM). Hence, these results clearly indicate that the hydrophobic behaviour of methylatedpillar[5]arene moiety can be exploited to create self-assembled architectures when connected to hydrophilic polymers. The critical aggregation concentration (CAC) in water was estimated to be 0.5 mg mL$^{-1}$ based on the dependence of the fluorescence intensity of MePilla-PDMAC versus its concentration (Fig. S13†).

Interestingly, VT-DLS experiments performed on MePilla-PDMAC and its complex MePilla-PDMAC-G2 indicated that both complex formation and temperature had no effect on the size distribution of micelles (Fig. S14†). Therefore, taking into account that above 340 K, VT-NMR ($^1$H) experiments performed (at the same concentration as the VT-DLS measurements) on MePilla-PDMAC-G2 (Fig. 5B) indicated the dissociation of the complex, and that VT-DLS investigations demonstrated the persistence of micelles upon heating, the micelle-like architectures prepared from MePilla-PDMAC appear to have the propensity to bind, and then to release on demand upon heating, the electron deficient guest G2 (Fig. 6C).

Conclusions

In conclusion, we have described the synthesis of a trithiocarbonate type RAFT agent incorporating a partially methylated pillar[5]arene moiety. By using this specifically designed RAFT agent, the polymerisation of DMAC was found to be controlled, affording a well-defined dimethylpillararene end-decorated PDMAC. This polymer has the ability to recognize, in a reversible manner, electron deficient guests both in organic and aqueous media. Furthermore, the hydrophobic nature of the pillararene unit has permitted the self-assembly of MePilla-PDMAC in water into micelle-like aggregates displaying reversible recognition properties. Since the RAFT procedure may be applied to the synthesis of a range well-defined macromolecular architectures, this study paves the way for the development of other pillararene-polymer conjugates with new applications.

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Notes and references


