



# Synthesis, Characterization, and Self-Assembling Properties of New Amphiphilic Dendrons Bearing Branched TRIS-Derived Oligomers as Polar Head Groups

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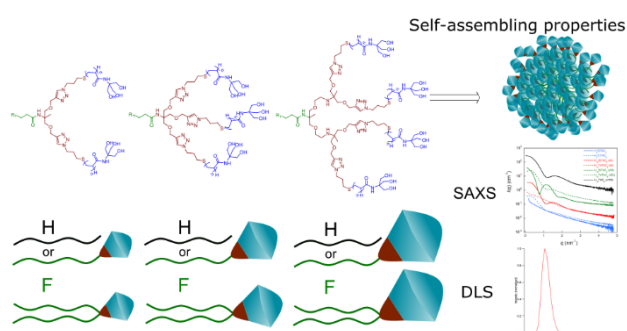
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# Synthesis, characterization and self-assembling properties of new amphiphilic dendrons bearing branched TRIS-derived oligomers as polar head groups

*Stéphane Desgranges, Valentin Lacanau, Françoise Bonneté, Marine Soulié, Frédéric Bihel, Damien Bourgeois, Christiane Contino-Pépin\**



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## ABSTRACT

The synthesis and characterization of a new family of dendritic surfactants called Dendri-TAC is described. Two series of single or double-tailed surfactants containing hydrophobic hydrocarbon or fluorocarbon chains grafted onto Tris(hydroxymethyl)aminomethane (or TRIS)-derived oligomeric polar heads, via a copper (I)-mediated click reaction, have been prepared. A total of thirteen new dendritic surfactants have been obtained by grafting linear polyTRIS branches of variable average degree of polymerization ( $DP_n$ ) onto a single or double-tailed fluorinated or hydrocarbon chain of variable length, via a dendritic central scaffold of generation  $G_1$  or  $G_2$ . Structural parameters of the surfactant assemblies in solution (radii of gyration ( $R_G$ ), volume-weighted hydrodynamic radii ( $R_H$ ) and aggregation numbers ( $N_{ag}$ )) were assessed by small-angle X-ray scattering (SAXS) and dynamic light scattering (DLS). Overall,

regardless of their tree-like structure (*i.e.* generation type), length of the headgroup (DP<sub>n</sub>) and nature (hydrocarbonated or fluorinated, single or double-tail) or length of the hydrophobic chains, self-assembling properties of H/F-DendriTACs are in agreement with usual trends of surfactant assemblies, *e.g.*, as a function of chain length or polar head volume. Thus, thanks to their great structural versatility, H/F-DendriTACs can provide highly tunable self-assembly morphologies that can be adapted to specific applications.

## INTRODUCTION

Amphiphilic molecules are ubiquitous in everyday life as they can be found in cosmetic formulations,<sup>1</sup> food, pharmaceutical,<sup>2</sup> ink, paint, and coating industries.<sup>3-5</sup> Bearing both hydrophobic and hydrophilic parts, they exhibit interfacial activity and self-assemble into supramolecular structures. The features of the latter rely on numerous factors such as the nature and size of both hydrophobic and hydrophilic domains, their concentration, etc.<sup>2, 4</sup> Depending on the nature of their polar head, amphiphiles can be classified as ionic or nonionic, the latter being of particular interest for biomedical applications as their structure does not change with pH and as they mainly produce biocompatible particles.<sup>6</sup> For many years our team has been developing biocompatible amphiphiles called TAC-surfactants comprising a Tris(hydroxymethyl)aminomethane-functionalized polyACrylamide (TAC) backbone as a nonionic polar head. Synthesized in one step by free radical telomerization of the Tris(Hydroxymethyl)AcrylamidoMethane (THAM) monomer,<sup>7, 8</sup> TAC-surfactants have been used in a wide range of biomedical applications such as drug delivery and protein stabilization.<sup>9</sup>

<sup>10</sup> The use of an aliphatic hydrocarbon (H) or a fluorinated (F) tail of variable length leads to H- and F-TAC surfactants respectively. In both cases the hydrophobic tail acts as a transfert reagent (or telogen) during the THAM telomerization, giving rise to a linear polar head, composed of a variable number of water-soluble tris(hydroxymethyl)aminomethane (TRIS)

units (see Figure 1). The so-called polyTRIS head is a linear oligomer, which is assumed to wrap around itself and be an interesting alternative to polyethylene glycol (PEG) or to sugar-based polar heads.

Although F- and H-TACs are easy to prepare at the gram scale their synthesis suffers from a growing lack of batch-to-batch reproducibility as the intended size of the polyTRIS head (average degree of polymerization (DP<sub>n</sub>)) increases. Moreover, while for the F-TAC series the DP<sub>n</sub> is precisely assessed by <sup>19</sup>F-NMR titration using an external reference,<sup>8</sup> for H-TAC analogues the DP<sub>n</sub> is estimated by <sup>1</sup>H-NMR by comparing the area of the signal due to the methyl group of the hydrocarbon tail with that of hydroxyl groups of TRIS units. Thereby, the longer the polyTRIS moiety the lesser accurate is the DP<sub>n</sub> estimation in that case.

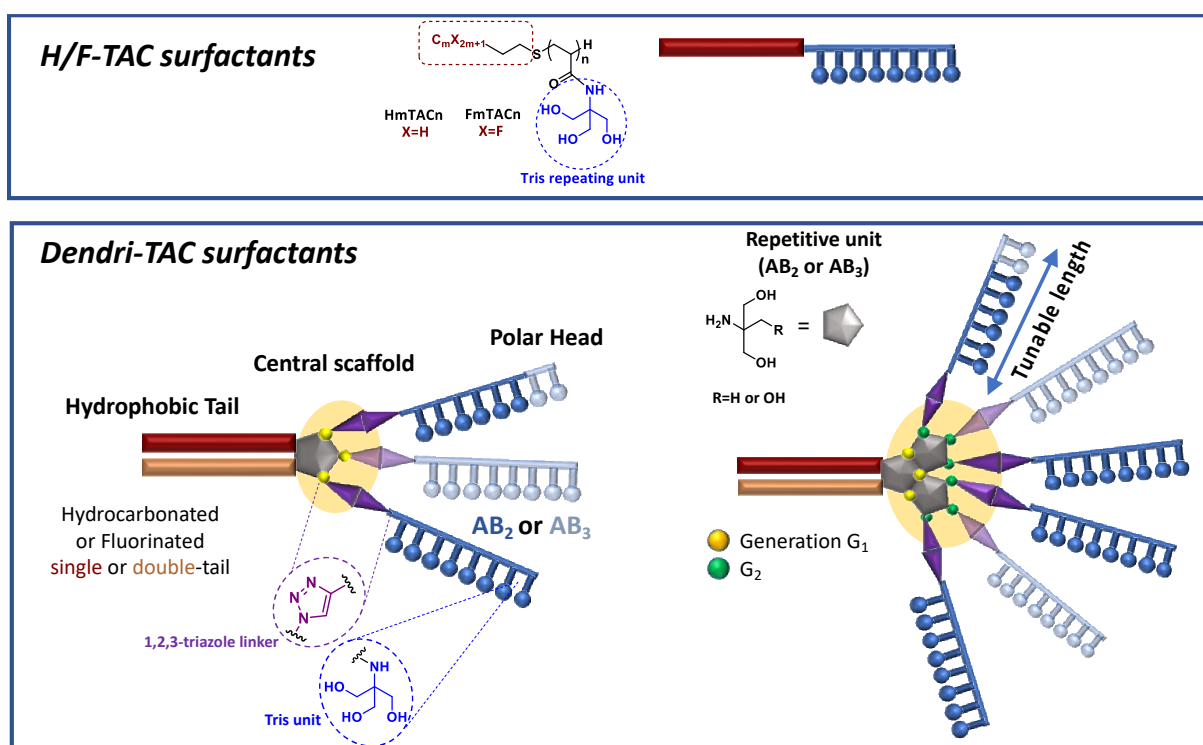
In order to overcome these drawbacks (structural variability, polydispersity, DP<sub>n</sub> estimation for polyTRIS of high DP<sub>n</sub>) keeping the main advantages of F- and H-TACs (high water solubility arising from the polyTRIS polar head, biocompatibility, modular structure), we have recently developed a new class of dendritic surfactants bearing dendronized PolyTRIS oligomers of short DP<sub>n</sub> (DP<sub>n</sub><15) as polar head groups.

Dendrimers and dendrons have drawn considerable attention because of their well-defined molecular structure resulting in unique three-dimensional architecture and small hydrodynamic radius.<sup>11</sup> One subclass are nonionic amphiphilic dendrons.<sup>12, 13</sup> This subclass has been extensively exemplified by the work of Haag et al, who developed a series of [hydrogenated or fluorinated glycerol-based dendrons and studied the influence of structural features on their self-assembly](#).<sup>14, 15</sup>

In comparison with F/H-TACs, which are linear oligomers whose structural modularity is limited to the length of both polar and apolar parts, dendronization is expected to increase the surface functionalization, hence the polar head volume, due to steric hindrance at the hydrophilic surface.

Design and preparation of these new dendritic surfactants, called Dendri-TACs, have been envisioned by the grafting of dendronized polyTRIS oligomers as polar head groups to single or double-tail apolar chains using click chemistry (Scheme 1). Such a synthetic pathway should provide high structural versatility combined with a well-defined, tunable and controlled preparation. By doing so, it is possible to easily tune both their hydrophilic tree-like arms structure *i.e.* both the number and the length (number average degree of polymerization, DP<sub>n</sub>) of hydrophilic branches, and to control the structure of their hydrophobic tail (single or double-tail, fluorinated or hydrocarbon chains of variable length). The central scaffold possesses a dendritic structure with multiple branching points depending on the dendron's generation (G<sub>n</sub>) and on the valence (2 or 3) of the repetitive unit (denoted AB<sub>2</sub> or AB<sub>3</sub> respectively, see Scheme 1) used to build the scaffold, *i.e.* 2-amino-2-methylpropane-1,3-diol (AB<sub>2</sub> unit) or tris(hydroxymethyl)aminomethane (AB<sub>3</sub> unit).

**Figure 1.** General structure of H/F-TAC and of Dendri-TAC surfactants



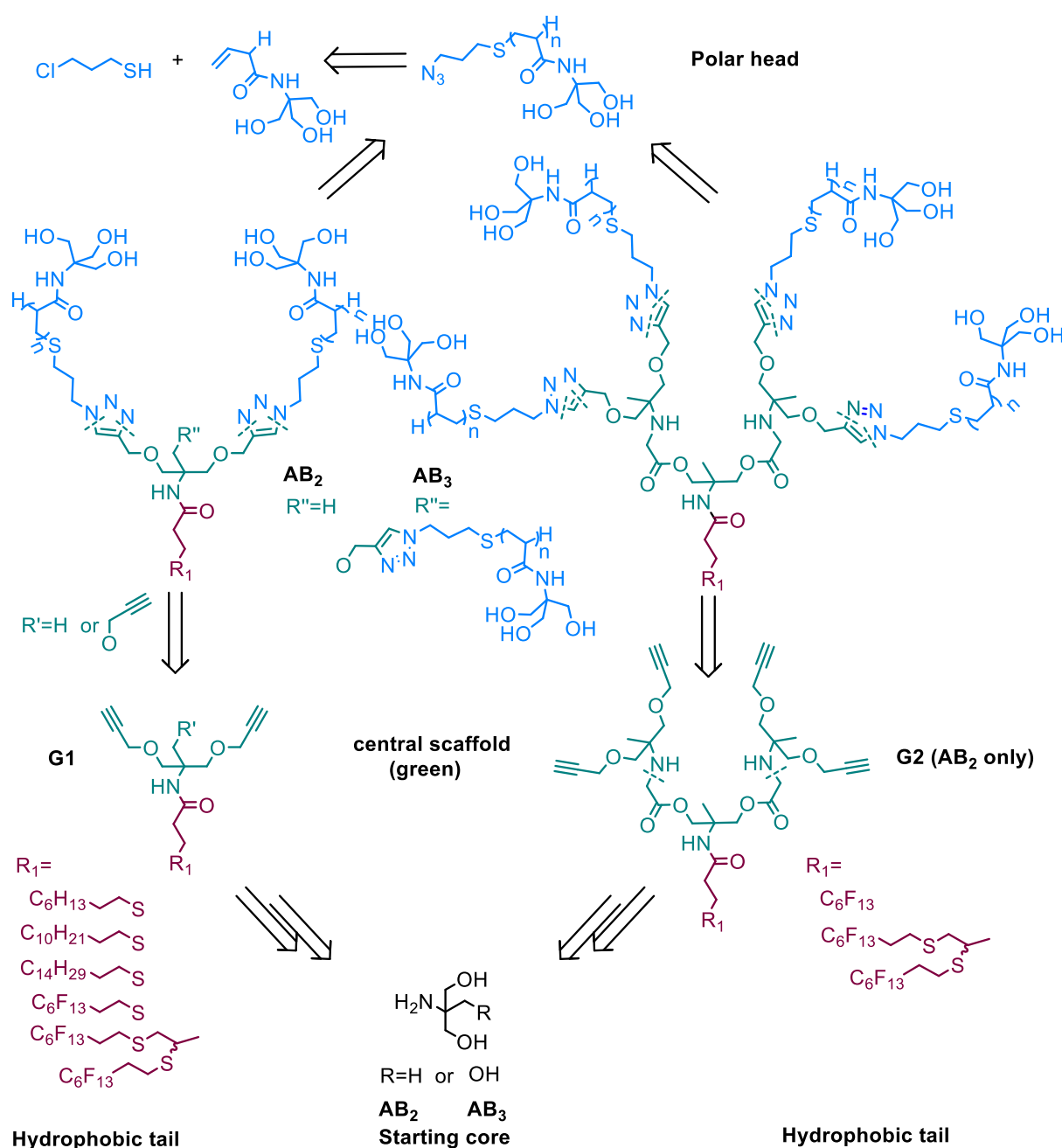
Herein, we report the synthesis of two generations of Dendri-TAC surfactants, along with the study of their structural features. AB<sub>2</sub> and AB<sub>3</sub> building blocks were used for the synthesis of G<sub>1</sub> Dendri-TACs, leading to either a di- or a tri-branched polar head. G<sub>2</sub> Dendri-TACs were synthesized using AB<sub>2</sub> units resulting in a tetra-cephalic polar head (See Scheme 1). The influence of structural features of the surfactant on the size and number of aggregation ( $N_{ag}$ ) of resulting self-assembled architectures was studied by DLS and SAXS analyses.

## RESULTS AND DISCUSSION

**Synthesis.** The Dendri-TAC surfactant family was built following a divergent synthetic approach starting from a bifunctional repetitive unit (starting core) endowed on one side (branching point B) with hydroxyl groups convertible to propargyl ones, in order to introduce the polar head via a copper (I) catalyzed azide-alkyne cycloaddition reaction (CuAAC), and on the other side (branching point A) an amino group graftable to the hydrophobic tail (HT).<sup>16</sup> Retrosynthetically, the structure of Dendri-TAC molecules can be divided in 3 fragments, including the HT, the central scaffold (made of AB<sub>3</sub> or AB<sub>2</sub> units) and the polar head. Each functional block can be varied separately, sequentially coupled and reused to easily grow the library thanks to a modular synthetic strategy (See Scheme 1). This approach allows to provide a series of structurally versatile surfactants. The synthesis is based on three key steps. First, the synthesis of the oligomeric polyTRIS polar head functionalized with an azido group. Secondly, the modular synthesis of apolar propargyl building blocks resulting from the combination of the central scaffold with the HT. Finally, the conjugation of the two former synthons through a 1,2,3-triazole junction after a Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. For the G<sub>1</sub> generation, three hydrocarbonated and two fluorinated tails of different length were

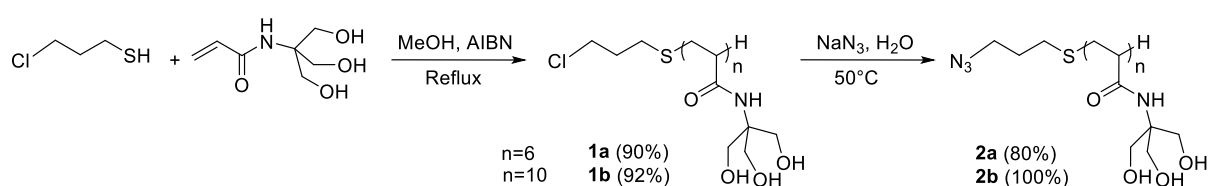
introduced:  $C_8H_{17}$ ,  $C_{12}H_{25}$ ,  $C_{16}H_{33}$  respectively called  $H_8$ ,  $H_{12}$  and  $H_{16}$  for the hydrocarbon series, and  $C_6F_{13}$  (single-tail) or  $diC_6F_{13}$  (double-tail) respectively called  $F_6$  and  $diF_6$  for the fluorinated one, with either  $AB_2$  or  $AB_3$  starting cores. For the  $G_2$  generation, single- ( $F_6$ ) or double-tail ( $diF_6$ ) fluorinated surfactants were prepared starting from a  $AB_2$ -type core.

**Scheme 1.** Retrosynthetic pathway of Dendri-TAC surfactants



**Synthesis of azido-polyTRIS.** Hydrosoluble polar heads, constituted of oligomeric polyTRIS moieties functionalized with azido groups, were easily synthesized in two steps. The first step consists in a free radical telomerization of THAM monomer, performed in methanol with chloropropanethiol as transfert agent and 2,2'-azobisisobutyronitrile (AIBN) as radical initiator. Then, an azido group is introduced by nucleophilic substitution of the chlorine atom in water. According to the choice of initial monomer/telogen molar ratio ( $1/R_0$ ), the number of  $n$  repeating TRIS units ( $n=DP_n$ ) can be adjusted. Two  $1/R_0$  ratios were intended namely 5 and 12. After a purification step by size exclusion chromatography, the resulting  $DP_n$  of azido-polyTRIS oligomers were assessed by  $^1H$ -NMR, and found to be of 6 and 10 for compounds **2a** and **2b** respectively (see Scheme 2). This slight drift of the  $DP_n$  values arises from the fact that free radical telomerization does not offer the same level of  $DP_n$  control as living polymerization techniques. However, it is a simpler, low-cost and more straightforward synthetic methodology.<sup>17</sup>

**Scheme 2.** Synthetic pathway of azido-polyTRIS oligomers

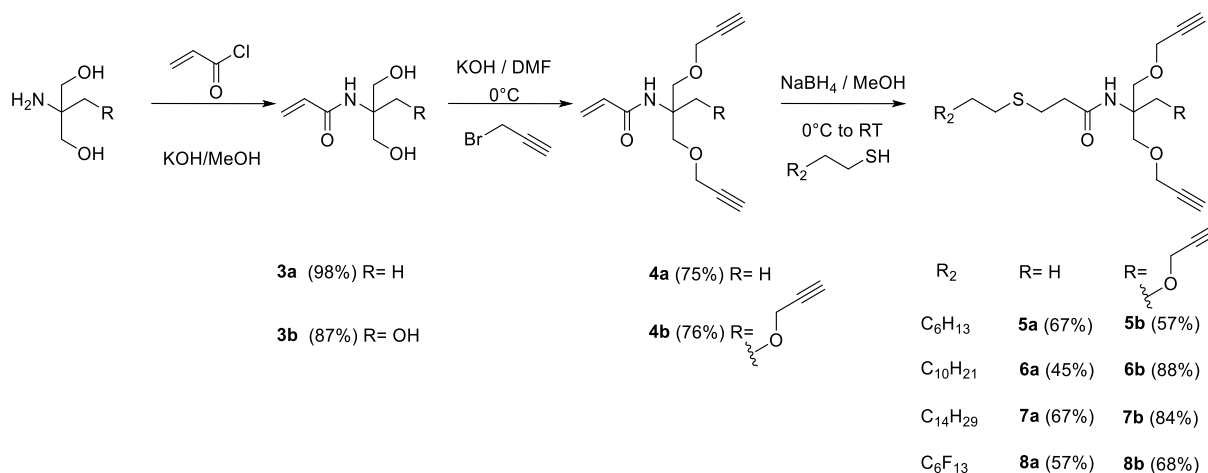


**Synthesis of apolar building blocks.** For all surfactants, the amino group of the AB<sub>2</sub> or AB<sub>3</sub> central scaffold is the anchor point of the HT through an amide junction. As shown in scheme 3, for single-tail analogues the amino group of the starting material (2-amino-2-methylpropane-1,3-diol or tris(hydroxymethyl)aminomethane) was first grafted to an acryloyl moiety (compounds **3a** and **3b**) followed by the propargylation of hydroxyl groups and consecutive thiol-ene Michael addition of intermediates (compounds **4a** and **4b**) to commercially available



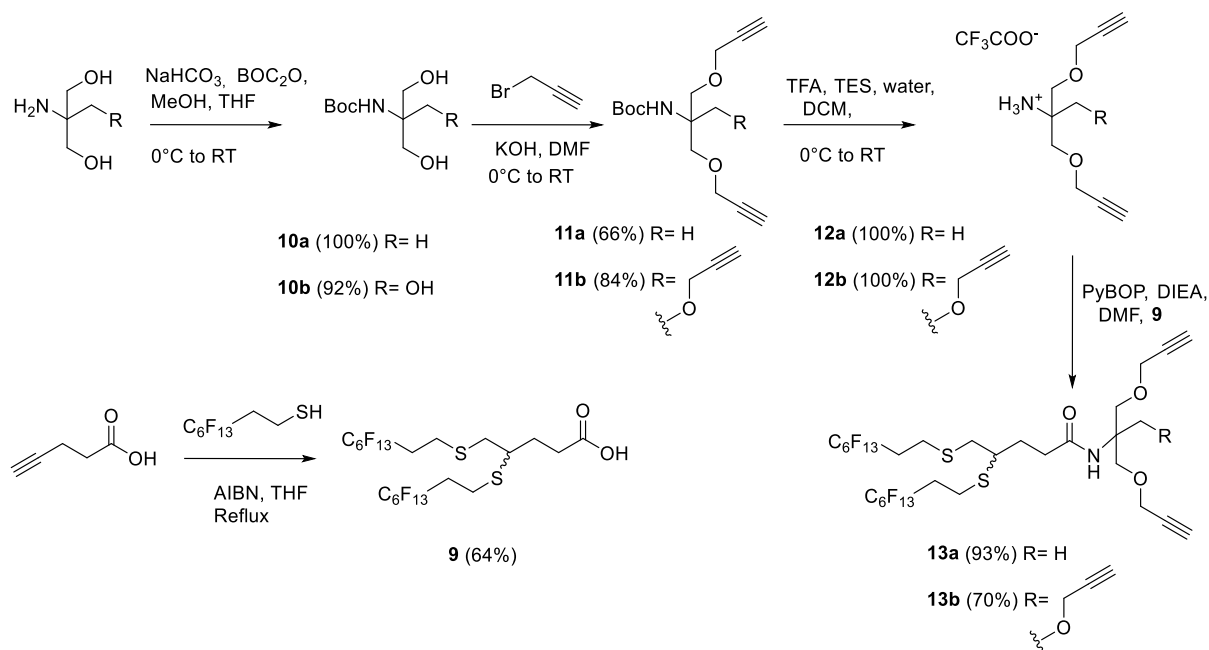
alkyl ( $\text{C}_6\text{H}_{13}\text{SH}$ ,  $\text{C}_{10}\text{H}_{21}\text{SH}$ ,  $\text{C}_{14}\text{H}_{29}\text{SH}$ ) or fluoroalkyl thiols ( $\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4\text{SH}$ ). Apolar single tails resulting from these three steps were referred as  $\text{H}_8$ ,  $\text{H}_{12}$ ,  $\text{H}_{16}$  and  $\text{F}_6$ , respectively (on compounds **5 a-b** to **8 a-b**).

**Scheme 3.** Synthetic pathway of single-tail apolar building blocks for  $\text{G}_1$  DendriTACs



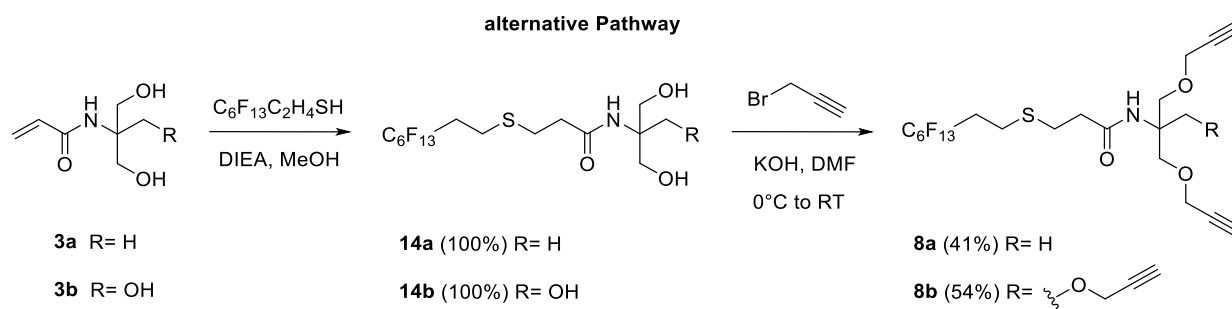
The synthesis of double-tail fluorinated surfactants (compounds **13a** and **13b**) is described in Scheme 4. The synthesis consists in the preparation of propargyl analogues of 2-amino-2-methylpropane-1,3-diol and of tris(hydroxymethyl)aminomethane as previously described by Chabre *et al*<sup>18</sup> and their consecutive coupling to a double-tail acid (compound **9**) under classical conditions of peptide synthesis. The latter double-tail acid being obtained in parallel by the thiol-yne click reaction of an alkynyl carboxylic acid with an alkyl or fluoroalkyl thiol, namely 4-pentynoic acid and 2-perfluorohexylethyl thiol herein. This dihydrothiolation reaction, conducted under radical conditions using AIBN, demonstrates remarkable robustness, versatility, and compatibility with a diverse range of functional groups.<sup>19</sup>

**Scheme 4.** Synthetic pathway of double-tail apolar building blocks for  $\text{G}_1$  DendriTACs



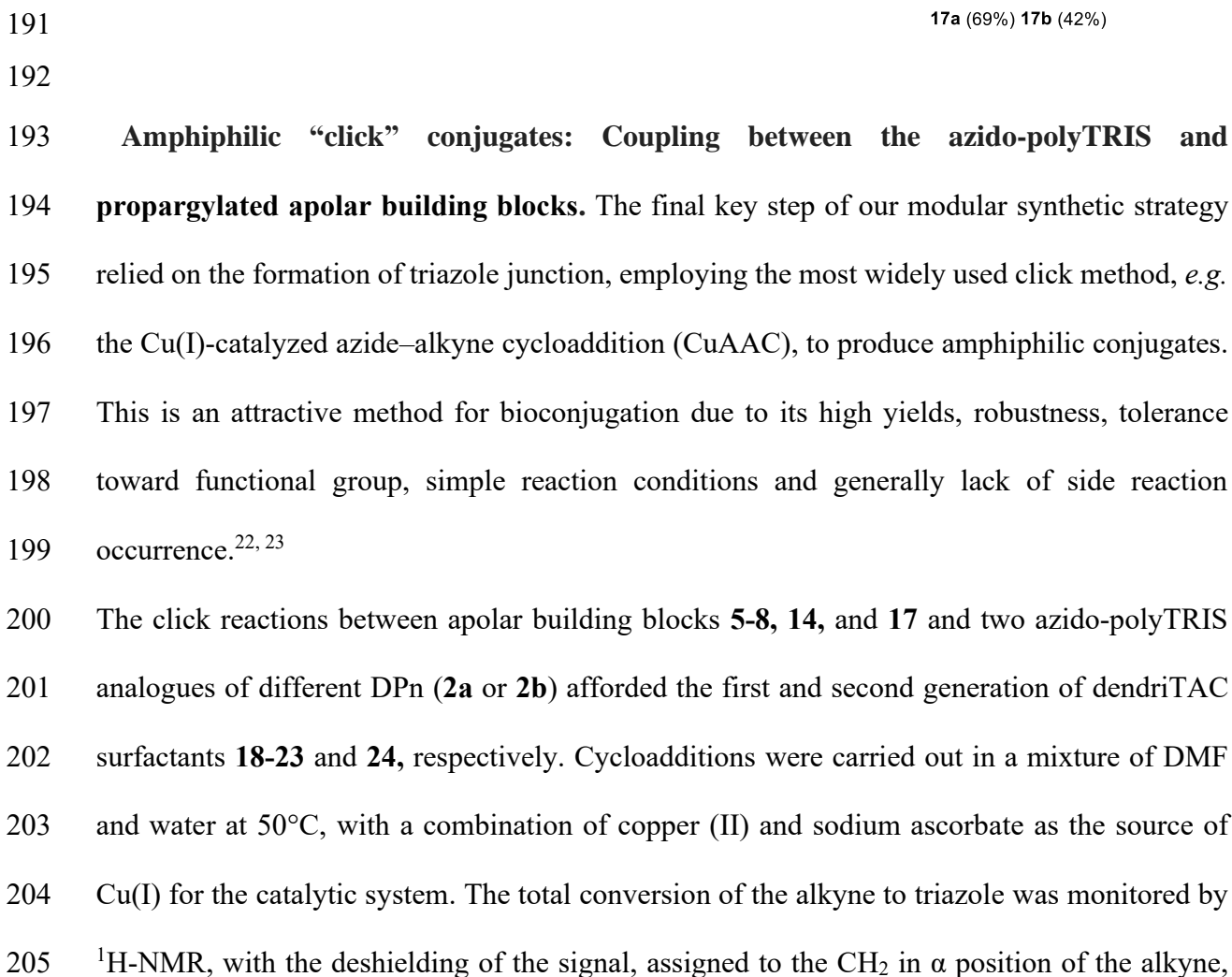
159  
 160 An alternative synthetic pathway for the G1 apolar building block was also followed in order  
 161 to prevent thiol-yne side additions and improve the overall yield. Hence, a Michael addition  
 162 was first performed on compounds **3a** and **3b** before the introduction of propargyl groups, as  
 163 shown in scheme 5. The addition was achieved in presence of a catalytic amount of Hunig's  
 164 base to obtain compounds **14a** & **14b** in quantitative yield. It is noteworthy that this reaction  
 165 condition (methanolic N,N-Diisopropylethylamine) allowing a quantitative Michael addition  
 166 on **3a** and **3b** completely failed when performed on compounds **4a** and **4b**. However, lower  
 167 yields were obtained for the following Williamson reaction compared to the original pathway  
 168 described on scheme 3, with 41 % & 54 % yield against 75% & 76% yield respectively. This  
 169 result may be due to the retro-Michael reaction that may have occurred under basic conditions  
 170 or prolonged reaction time.<sup>20, 21</sup> Overall yields were actually close, with 43% & 52% for the  
 171 original pathway against 41% & 54% for the alternative pathway.

172 **Scheme 5.** Alternative synthetic pathway of G1 apolar building blocks (single-tail)



**DendriTAC second generation (G<sub>2</sub>).** To build the apolar building blocks for the synthesis of G<sub>2</sub> DendriTACs, an approach comprising an ester bond was applied as shown in scheme 6 consisting in 3 steps. Only AB<sub>2</sub> repetitive units were used in order to limit steric hindrance and repulsive interactions between oligomeric branches. The HT was either constituted of commercially available 1H, 1H, 2H, 2H-perfluorononanoic acid or with the previously synthesised fluorinated double-tail acid **9**. These HT and the AB<sub>2</sub> starting core were combined through a peptide coupling, using EEDQ in ethanol at reflux, to obtain the diols **15a** and **15b** in 63% and 83% yield respectively. The second step involves the acylation of these diols with the 2-chloroacetyl chloride in DMF for the single-tail analogue and THF for the double-tail one, in order to overcome solubility problems observed with DMF for the latter, to afford the dichloride **16a** and **16b** in close yields, namely 84% and 81%. Then, compounds **16a** and **16b** underwent the Finkelstein reaction to promote the nucleophilic substitution of chlorides with the di-propargyl **13a** affording the G<sub>2</sub> apolar building blocks **17a** and **17b** in 69% and 42 % yield respectively.

**Scheme 6.** Synthetic pathway of apolar building blocks for G<sub>2</sub> DendriTACs

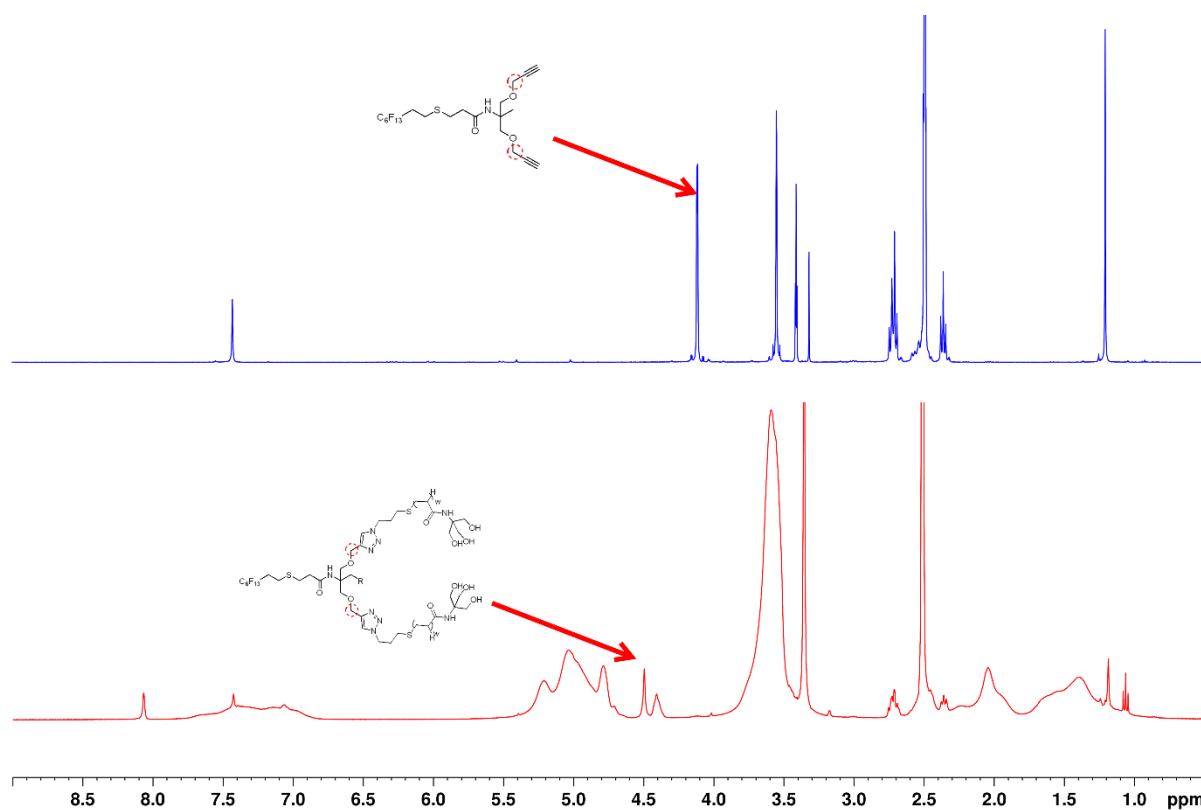


**Amphiphilic “click” conjugates: Coupling between the azido-polyTRIS and propargylated apolar building blocks.** The final key step of our modular synthetic strategy relied on the formation of triazole junction, employing the most widely used click method, *e.g.* the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), to produce amphiphilic conjugates. This is an attractive method for bioconjugation due to its high yields, robustness, tolerance toward functional group, simple reaction conditions and generally lack of side reaction occurrence.<sup>22, 23</sup>

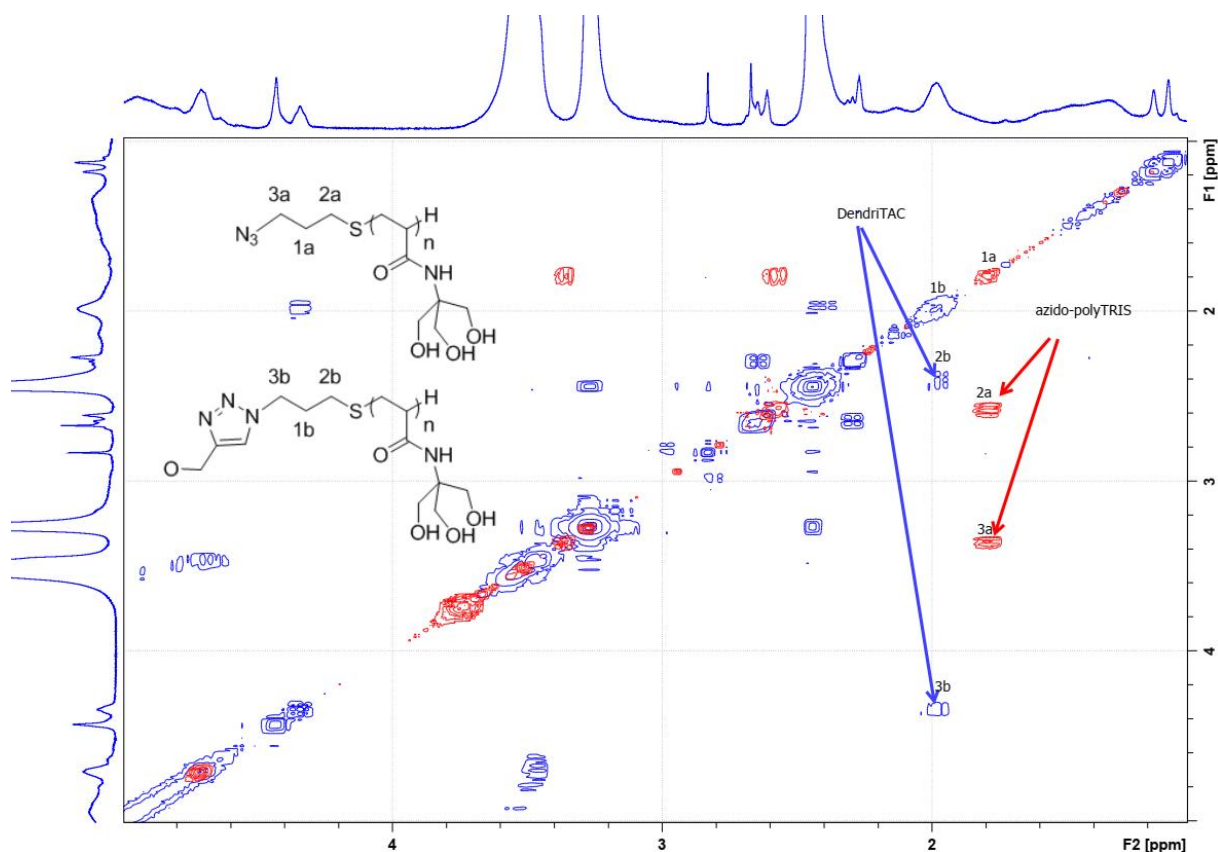
The click reactions between apolar building blocks **5-8**, **14**, and **17** and two azido-polyTRIS analogues of different DPn (**2a** or **2b**) afforded the first and second generation of dendriTAC surfactants **18-23** and **24**, respectively. Cycloadditions were carried out in a mixture of DMF and water at 50°C, with a combination of copper (II) and sodium ascorbate as the source of Cu(I) for the catalytic system. The total conversion of the alkyne to triazole was monitored by <sup>1</sup>H-NMR, with the deshielding of the signal, assigned to the CH<sub>2</sub> in α position of the alkyne,

from  $\delta = 4.12$  ppm to  $\delta = 4.54$  ppm after the triazole formation (see Figure 2). Both F- and H-DendriTAC surfactants were purified by size exclusion chromatography (SEC) on a Sephadex LH-20 column with MeOH as eluent. The F-DendriTAC series was consecutively purified by fluororous solid phase extraction (FSPE). The main impurity was the unreacted azido-polyTRIS. Hence, to confirm its removal during the purification process, a 2D  $[1H,1H]$  COSY NMR experiment was conducted, as signals of this unreacted azido-polyTRIS were overlapping with signals from the newly formed amphiphilic click conjugates on  $^1H$ -NMR spectra. The total disappearance of cross peaks of coupled protons at  $\delta = 1.78$  ppm, ascribed to the three methylene groups of the terminal propyl chain of the azido-polyTRIS (**1a**, **2a** & **3a** in Figure 3) was observed. As shown in Table 1, except for compound **20a**, purified DendriTACs showed a slight increase in DP<sub>n</sub> compared to starting azido-polar heads **2a** (DP<sub>n</sub> = 6) or **2b** (DP<sub>n</sub> = 10). This DP<sub>n</sub> shift can arise from the fractionation of DendriTACs, during the final LH-20 purification step. According to the Sephadex column features (column volume, packing...) the molecular size distribution of these branched molecules can be refined compared to starting linear oligomers **2a** and **2b**, thus leading to collected fractions of interest exhibiting new DP<sub>n</sub> values. It is also noteworthy that DendriTACs of low DP<sub>n</sub> and unreacted azido-polyTRIS analogues of high DP<sub>n</sub> can coelute during the size exclusion chromatography which contributes to limit some reaction yields from 20% to 70%. For the second generation, the low yields obtained might be due to the ester hydrolysis that may have occurred during the coupling or purification steps.

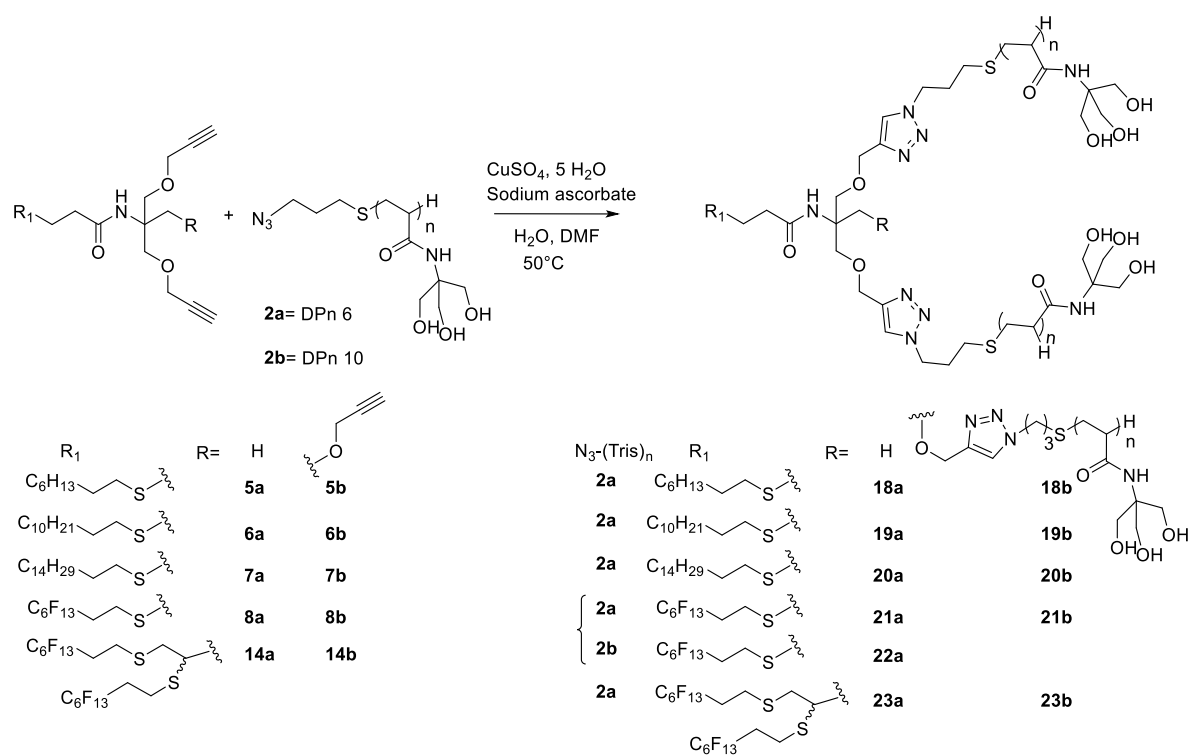
**Figure 2.** Click reaction monitoring. *Above:* example of  $^1H$ -NMR spectrum of a fluorinated HT central core. *Below:*  $^1H$ -NMR spectrum of a total reaction completion.



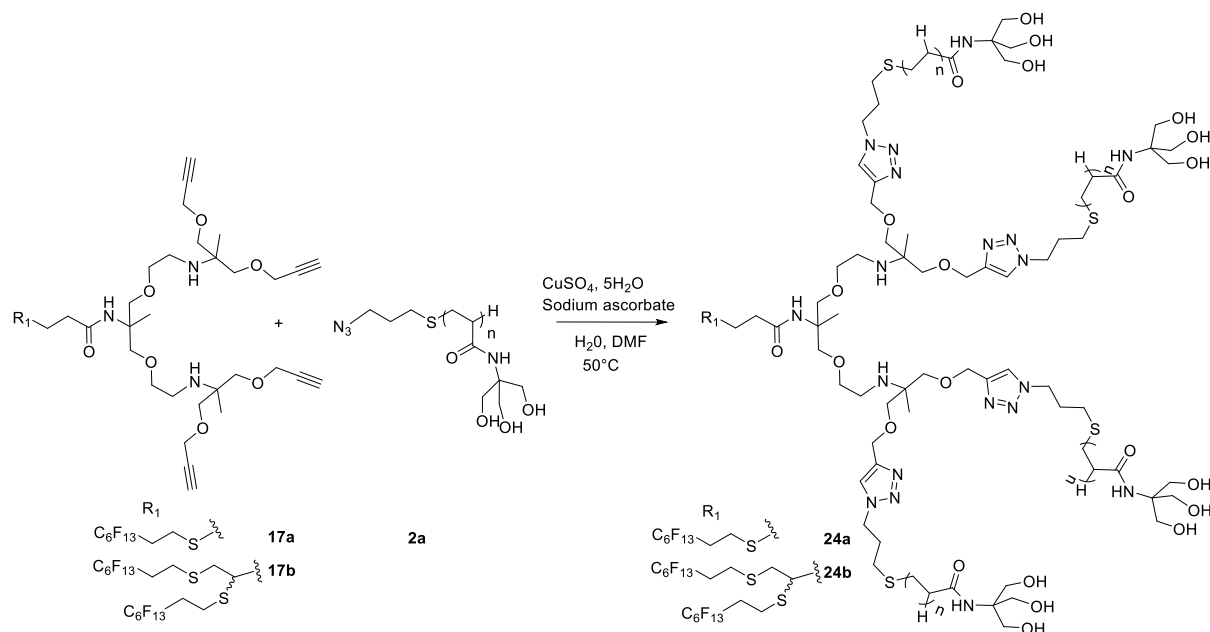
**Figure 3.** Overlay of 2D [1H,1H]-COSY NMR spectrum, in blue propargylated apolar moiety spectrum and in red a DendriTAC spectrum (F<sub>6</sub>DiTAC<sub>6</sub>) after purification



**Scheme 7.** Click reaction for G<sub>1</sub> DendriTAC surfactants' synthesis



**Scheme 8.** Click reaction for G<sub>2</sub> DendriTAC surfactants' synthesis



**Table 1.** Surfactants' synthesis summary and characterization

G	HT <sup>1</sup>	PH <sup>2</sup>	Ref	Yield <sup>3</sup>	DP <sub>n</sub>	Surfactant	M <sub>n</sub> <sup>4</sup> ( <sup>1</sup> H-NMR) g/mol	M <sub>n</sub> <sup>5</sup> (GPC) g/mol	D <sub>M</sub> <sup>6</sup>
G <sub>1</sub>	5a	2a	18a	30%	9	H <sub>8</sub> DiTAC <sub>9</sub>	3769	2170	1.11
G <sub>1</sub>	6a	2a	19a	63%	9	H <sub>12</sub> DiTAC <sub>9</sub>	3824	1940	1.11
G <sub>1</sub>	7a	2a	20a	22%	3	H <sub>16</sub> DiTAC <sub>3</sub>	1779	N/A <sup>7</sup>	N/A
G <sub>1</sub>	8a	2a	21a	20%	7	F <sub>6</sub> DiTAC <sub>7</sub>	3301	2282	1.13
G <sub>1</sub>	8a	2b	22a	73%	11	F <sub>6</sub> DiTAC <sub>11</sub>	4702	2094	1.13
G <sub>1</sub>	5b	2a	18b	43%	6	H <sub>8</sub> TriTAC <sub>6</sub>	3939	2226	1.12
G <sub>1</sub>	6b	2a	19b	41%	8	H <sub>12</sub> TriTAC <sub>8</sub>	5045	1919	1.14
G <sub>1</sub>	7b	2a	20b	29%	8	H <sub>16</sub> TriTAC <sub>8</sub>	5101	1921	1.16
G <sub>1</sub>	8b	2a	21b	65%	7	F <sub>6</sub> TriTAC <sub>7</sub>	3296	2420	1.11
G <sub>1</sub>	13a	2a	23a	56%	6	DiF <sub>6</sub> DiTAC <sub>6</sub>	3357	3208	1.06
G <sub>1</sub>	13b	2a	23b	80%	8	DiF <sub>6</sub> TriTAC <sub>8</sub>	4403	2290	1.17
G <sub>2</sub>	17a	2a	24a	31%	6	F <sub>6</sub> TetraTAC <sub>6</sub>	5592	2582	1.09



<b>G<sub>2</sub></b>	<b>17b</b>	<b>2a</b>	<b>24b</b>	<b>30%</b>	<b>6</b>	<b>DiF<sub>6</sub>TetraTAC<sub>6</sub></b>	<b>6058</b>	<b>3094</b>	<b>1.10</b>
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<sup>1</sup> HT: hydrophobic tail; <sup>2</sup> PH: Polar head; <sup>3</sup> Click reaction yield; <sup>4</sup> Number-averaged weights in g/mol determined by <sup>1</sup>H-NMR in DMSO-d<sub>6</sub>; <sup>5</sup> Number-averaged weights in g/mol determined by GPC; <sup>6</sup> Molar Mass Dispersities ( $\bar{D}_M = M_w/M_n$ );  $M_n$  and  $\bar{D}_M$  were determined by DMF (5mM LiBr) SEC against linear polystyrene standards. <sup>7</sup> N/A: not applicable

DendriTAC surfactants were analyzed by <sup>1</sup>H-NMR and by gel permeation chromatography (GPC), number-averaged molecular weights ( $M_n$ ) were determined by <sup>1</sup>H-NMR ( $M_n^4$ ) and by GPC ( $M_n^5$ ) while weight-averaged molecular weights ( $M_w$ ) and polydispersity ( $\bar{D}_M$ ) were assessed by GPC only. It is noteworthy that relatively narrow  $\bar{D}_M$  values, (comprised between 1.06 and 1.17) were obtained for DendriTACs (Table 1), meaning that the synthesis of azido-polyTRIS series somehow occurred in a controlled manner.

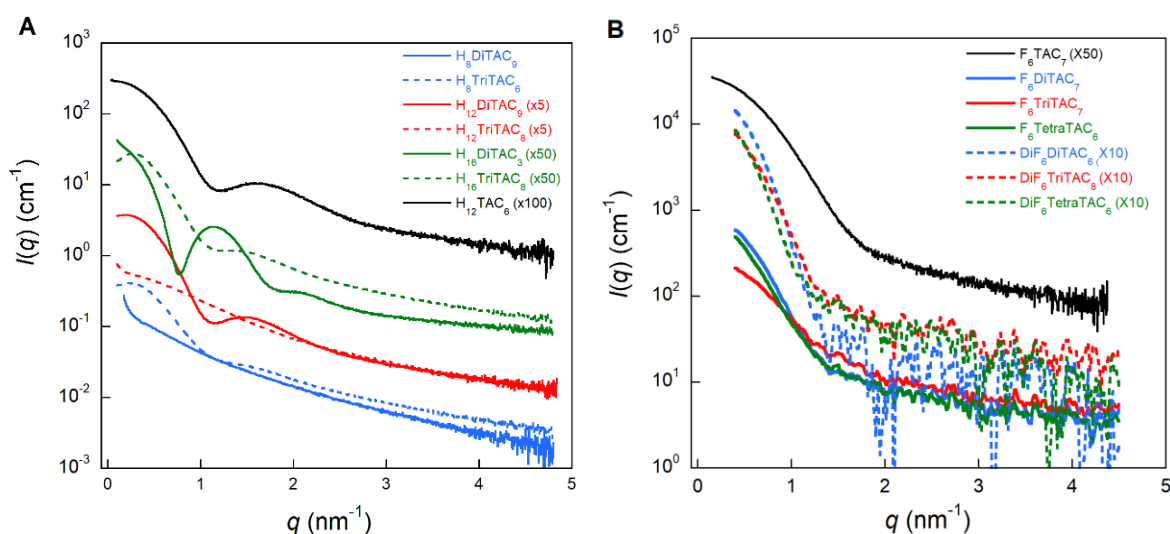
**Self-assembly studies.** DLS and SAXS experiments have been performed to characterize structural parameters, in terms of size, shape, aggregation number of this new family of hydrogenated and fluorinated surfactants in aqueous solution. H/F-DendriTACs were dissolved in Milli-Q water and studied as a function of surfactant concentration between 0.8 and 50 mg/mL to highlight changes in shape and/or intermicellar weak interactions. DLS experiments were conducted prior to SAXS in order to evaluate both polydispersity (PDI) of surfactant solutions and hydrodynamic radius ( $R_H$ ) of surfactant assemblies in solution. The PDI values of all compounds were found less than 0.2 suitable for SAXS experiments (see SI, Table S1). Indeed, SAXS analyses require quite monodisperse samples for reliable results. SAXS profiles are shown only at 20 or 25 mg/mL in Figure 4. SAXS patterns with concentration were measured only for H-DendriTACs (see SI, Figure S4) due to the low quality of SAXS curves (ratio signal/noise) for F-DendriTACs at low concentrations. For all H/F-DendriTACs, the radius of gyration ( $R_G$ ) was determined from the linear Guinier approximation  $\ln I(q) = \ln I(0) - (qR_G)^2/3$  at very small angles, *i.e.* such that  $qR_G < 1.3$ ) and the maximum micelle dimension ( $D_{max}$ ) from the pair distribution function (PDF) by Inverse Fourier Transformation of the

scattering intensity using the program GNOM<sup>24</sup> (see SI, Figure S2A). A Kratky representation (*i.e.* a plot  $q^2 I(q)$  as function of  $q$ ) was also performed to evaluate if the assemblies were globular, flexible or non-assembled. The aggregation number  $N_{ag}$ , *i.e.* the number of surfactant molecule per surfactant assembly, was finally determined from the absolute forward intensity,  $I(0)$  in  $\text{cm}^{-1}$ , *via* the expression:

$$N_{ag} = N_a \frac{I_{\text{surf}}(0)}{M_{\text{mono}} \cdot c [r_0 \cdot v_p \cdot (\rho_{\text{surf}} - \rho_0)]^2}$$

with  $N_a$  the Avogadro's number,  $v_p$  the specific volume of surfactant ( $\text{cm}^3/\text{g}$ ),  $\rho_{\text{surf}}$  and  $\rho_0$  the electron scattering length densities ( $\text{e}^-/\text{cm}^3$ ) of surfactant and water respectively,  $M_{\text{mono}}$  the molar mass of each surfactant monomer,  $r_0$  the classical electron radius equal to  $0.28179 \cdot 10^{-12} \text{ cm/e}^-$ . The partial specific volumes,  $v_p$ , were calculated from chemical composition.<sup>25</sup> All structural parameters are listed in table 2.

**Figure 4:** SAXS profiles,  $I(q)$  versus  $q$ , for H-DendriTAC (A) at 25 mg/mL ( $\text{H}_8$ -Di & TriTAC,  $\text{H}_{12}$ -Di & TriTAC) and 20 mg/mL ( $\text{H}_{16}$ -Di & TriTAC), for F-DendriTACs (B) at 20 mg/mL. (The curves are shifted for more clarity:  $\times 5$ ,  $\times 10$ ,  $\times 50$ ,  $\times 100$  represents offset parameter of the curve from its original position)



**Table 2:** Structural parameters of H/F-DendriTAC assemblies obtained from SAXS and DLS analysis

Entry	Surfactant	DPn	Total TRIS units	$R_G$ nm (SAXS)	$D_{\max}$ nm (SAXS)	$R_H$ nm (DLS)	$N_{ag}$ (SAXS)
<b>H-DendriTACs<sup>†</sup></b>							
1	H <sub>8</sub> DiTAC <sub>9</sub>	9	18	2.20+/-0.05	7.5+/-0.5	1.5	3
2	H <sub>8</sub> TriTAC <sub>6</sub>	6	18	2.75+/-0.01	9.0+/-0.5	1.5	7
3	H <sub>12</sub> DiTAC <sub>9</sub>	9	18	3.05+/-0.01	8.7+/-0.3	3.5	20
4	H <sub>12</sub> TriTAC <sub>8</sub>	8	24	1.79+/-0.01	6.5+/-0.1	4.5	1
5	H <sub>16</sub> DiTAC <sub>3</sub>	3	6	4.19+/-0.01	10.4+/-0.1	5.2	21
6	H <sub>16</sub> TriTAC <sub>8</sub>	8	24	3.25+/-0.05	9.5+/-0.1	2.8	15
<b>F-DendriTACs<sup>‡</sup></b>							
7	F <sub>6</sub> DiTAC <sub>7</sub>	7	14	2.80+/-0.05	7.6+/-0.1	2.4	14
8	F <sub>6</sub> DiTAC <sub>11</sub>	11	22	3.10+/-0.05	9.9+/-0.1	3.3	9
9	F <sub>6</sub> TriTAC <sub>7</sub>	7	21	2.37+/-0.02	6.6+/-0.1	1.7	3
10	F <sub>6</sub> TetraTAC <sub>6</sub>	6	24	2.72+/-0.02	7.0+/-0.1	2.8	7
11	DiF <sub>6</sub> DiTAC <sub>6</sub>	6	12	3.50+/-0.05	9.5+/-0.5	4.6	37
12	DiF <sub>6</sub> TriTAC <sub>8</sub>	8	24	2.75+/-0.12	8.05+/-0.1	1.2	11
13	DiF <sub>6</sub> TetraTAC <sub>6</sub>	6	24	3.63+/-0.02	9.3+/-0.5	4.7	15
<b>H/F-TACs<sup>†</sup></b>							
14	H <sub>12</sub> TAC <sub>6</sub>	6	6	2.78+/-0.01	8.5+/-0.3	3.0	29
15	F <sub>6</sub> TAC <sub>7</sub>	7	7	2.37+/-0.01	7.7+/-0.1	2.5	13

Structural parameters for H/F-DendriTACs and H/F-TACs at 20-25 mg/mL; <sup>†</sup>these SAXS measurements were performed in a  $q$ -range of 0.032–4.93 nm<sup>-1</sup> on BM29 at ESRF; repulsive interactions at very small angles are clearly visible for some assemblies (entries 2, 3, 6). <sup>‡</sup> These SAXS measurements were performed in a  $q$ -range of 0.2–4.5 nm<sup>-1</sup> on a bench-top SAXS system at ICSM; no specific interactions are visible in this  $q$ -range.

296 From scattering experiments (Figure 4) we observe that H/F-DendriTACs form small  
297 globular assemblies in water regardless of their tree-like structure (*i.e.* generation type), length  
298 of the headgroup (DP<sub>n</sub>) and nature (hydrocarbonated or fluorinated, single or double-tail) or  
299 length of the hydrophobic chains. This is confirmed by the Kratky plots (See SI Figures S2B-  
300 C), which highlight a globular micellar structure as seen by a bell-shaped (Gaussian) peak for  
301 all H/F-DendriTACs at small  $q$  ( $< 1 \text{ nm}^{-1}$ ), except for H<sub>12</sub>TriTAC<sub>8</sub> and H<sub>8</sub>DiTAC<sub>9</sub>, which show  
302 a plateau at large  $q$  typical of non-globular or flexible objects. Some SAXS curves (for  
303 surfactants H<sub>12</sub>TAC<sub>6</sub>, H<sub>12</sub>DiTAC<sub>9</sub> and H<sub>16</sub>DiTAC<sub>3</sub> in Figure 4A) exhibit a distinct 2<sup>nd</sup> maximum  
304 in the intermediate  $q$ -region, whose value is inversely proportional to a size in the micelle. This  
305 peak, which is characteristic of a core-shell structure where a large difference in the scattering  
306 contrast exists between the polar head group and the apolar tail, is more pronounced for H-  
307 DendriTACs than for F-DendriTACs. In addition, regarding surfactants H<sub>8</sub>TriTAC<sub>6</sub>,  
308 H<sub>12</sub>DiTAC<sub>9</sub> and H<sub>16</sub>TriTAC<sub>8</sub>, the profile of scattering intensities recorded at small angles (*i.e.*  
309 low  $q$ -region) is clearly indicative of repulsive interactions between micelles (Figure 4/A). In  
310 table 2 are listed  $R_H$ , the micelle volume-weighted hydrodynamic radius determined by DLS,  
311  $R_G$  the radius of gyration and  $D_{\text{max}}$ , the maximum dimension of the DendriTAC assemblies,  
312 both determined by SAXS. For all surfactants,  $R_H$  and  $R_G$  are lower than 6 nm, and  $D_{\text{max}}$  remains  
313 below 11 nm. Compared to conventional surfactants,<sup>26</sup> all compounds present small aggregation  
314 numbers, except DendriTAC 4 (H<sub>12</sub>TriTAC<sub>8</sub>), which is a monomer form at this concentration  
315 in view of its low aggregation number ( $N_{\text{ag}} = 1$ ). Overall, self-assembling properties are in  
316 agreement with usual trends of surfactant assemblies, *e.g.*, as a function of chain length or polar  
317 head volume. However, the high degree of structural versatility of H/F-DendriTACs, which  
318 offers a wide range of aggregate morphologies, can be tailored to specific applications.

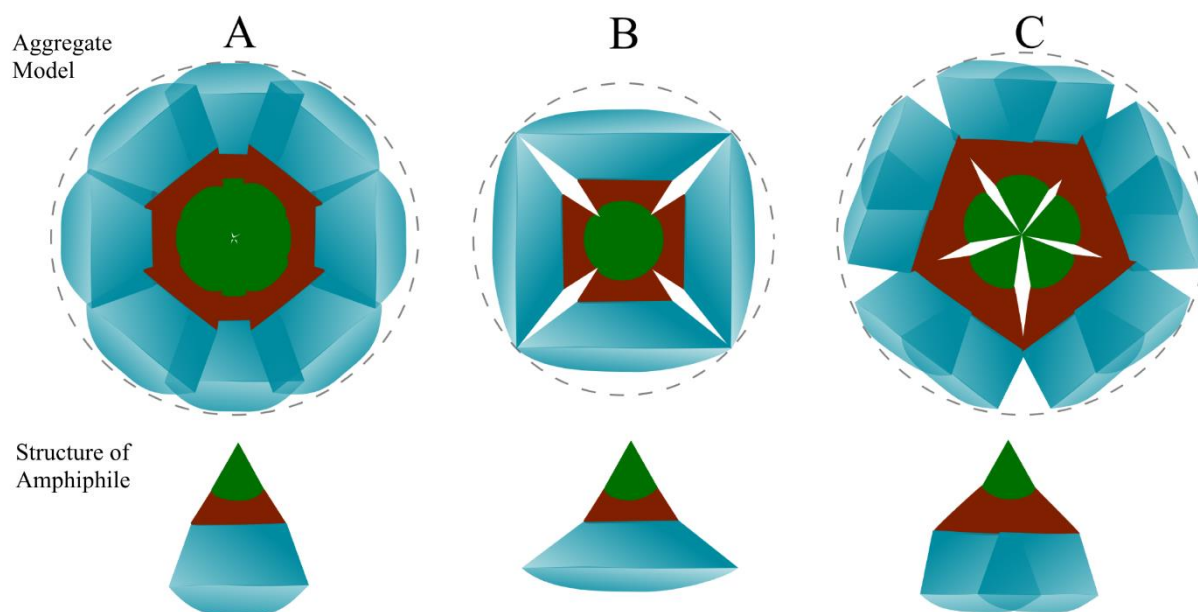
319 Regarding H-DendriTACs, for a defined headgroup, *i.e.* same length and tree-like structure  
320 (*e.g.* entries 1 & 3 and 4 & 6),  $N_{\text{ag}}$ ,  $R_G$  and almost all  $R_H$  values increase with the elongation of

321 the hydrophobic tail reflecting a better anchoring of monomers in the micelle due to higher  
 322 hydrophobic interactions between apolar chains, consistent with literature and previous  
 323 studies.<sup>27, 28</sup> The aggregation numbers approximatively increase by 15 monomers per micellar  
 324 aggregates for a group of four carbons added on the hydrocarbonated tail. Whereas for the same  
 325 tree-like structure, this extension of the hydrophobic tail (four carbons) is balanced by a  
 326 reduction in the length of the headgroup, *i.e.* DPn values, and leads to an equivalent aggregation  
 327 number (entries **3 & 5**). For the same apolar chain, the micelle size decreases with increasing  
 328 total number of TRIS units (entries **3 & 4** and **5 & 6**), which is achieved by adding a polar  
 329 branch from AB<sub>2</sub> to AB<sub>3</sub> with either comparable (entries **3 & 4**) or higher DPn values (entries  
 330 **5 & 6**). This is in agreement with the concept of molecular packing parameter  $P$  ( $P$  being  
 331 defined as  $V_o/a_e l_o$ , where  $V_o$  is the surfactant tail volume,  $l_o$  is the tail length, and  $a_e$  is the  
 332 equilibrium area per molecule at the aggregate surface) introduced by Israelachvili et al.<sup>29</sup> The  
 333 addition of several hydrated TRIS units (either by elongation or branching enhancement)  
 334 improves the repulsion between polyTRIS branches, leading to an increase in the polar head  
 335 volume and therefore in the equilibrium area  $a_e$ . This induces a decrease in the packing  
 336 parameter  $P$  leading to the formation of smaller objects. These repulsive interactions between  
 337 TRIS units at the surface of surfactants also contribute to repulsive interactions between  
 338 micelles clearly observable on SAXS curves in the case of H<sub>8</sub>TriTAC<sub>6</sub>, H<sub>12</sub>DiTAC<sub>9</sub> and  
 339 H<sub>16</sub>TriTAC<sub>8</sub> (entries **2, 3, 6**) at very small angles (*i.e.*  $q \rightarrow 0$ ) by a decrease in  $I(q)$ , which can  
 340 slightly underestimate  $R_G$  and forward intensity  $I(0)$  thus impacting assembly size and mass  
 341 values. It is noteworthy that for surfactants with both identical apolar chain length and same  
 342 total number of TRIS units, micelle size decreases with longer polyTRIS branches (entries **1 &**  
 343 **2**), the equilibrium area  $a_e$  due to repulsion between longer AB<sub>2</sub>-connected branches being  
 344 higher than for shorter AB<sub>3</sub> ones.

345 In the case of fluorinated surfactants, the latter repulsion is counterbalanced by an improved  
346 hydrophobic interaction between fluorinated chains, also referred as “fluorophilicity”,  
347 consistent with a closely-packed fluorinated core.<sup>30,31</sup> This leads to a decrease of the  
348 aggregation number (entries **8 & 9**). If we compare the evolution of the structural parameters  
349 from H<sub>8</sub>DiTAC<sub>9</sub> to H<sub>8</sub>TriTAC<sub>6</sub> (entries **1 & 2**) with those of fluorinated surfactants with the  
350 same carbon atoms number on the hydrophobic tail, namely from F<sub>6</sub>DiTAC<sub>11</sub> to F<sub>6</sub>TriTAC<sub>7</sub>  
351 (entries **8 & 9**), the trend between size and aggregation number is clearly reversed: for H<sub>8</sub>-  
352 DendriTACs (entries **1 & 2**) it seems that the repulsion between the polar heads (due to a  
353 combination of steric hindrance and strong hydration of hydroxyl groups) increases with the  
354 length of the polyTRIS chains and with the easier unfolding of these chains from AB<sub>3</sub> to AB<sub>2</sub>  
355 branching type. Then, from H<sub>8</sub>TriTAC<sub>6</sub> to H<sub>8</sub>DiTAC<sub>9</sub> (entries **2 & 1**) the aggregation number  
356 decreases and the size of micelles too. While for F<sub>6</sub>-DendriTACs, both hydrophobicity and  
357 lipophobicity of fluorinated chains, along with their lower conformational freedom (rigid rod-  
358 like chains) concur to a “super” hydrophobic binding interaction between F-chains (mainly  
359 driven by the entropic gain of water molecules in bulk water) and contribute to their ordered  
360 packing into the micelle core.<sup>30-32</sup> Their combination to bulky oligomeric head groups, probably  
361 confers a more conical shape to F-DendriTAC monomers with a more "classical" influence of  
362 the tree-like structure on the volume of the heads: AB<sub>3</sub> induces a greater curvature of the  
363 surfactant with stronger anchoring of fluorinated tails in the micelle core, resulting in smaller  
364 micelles when moving from AB<sub>2</sub> to AB<sub>3</sub>. The general trend observed from F<sub>6</sub>DiTAC<sub>11</sub> to  
365 F<sub>6</sub>TriTAC<sub>7</sub> (entries **8 & 9**) is that both the aggregation number and the micelle size decrease  
366 even though the AB<sub>2</sub> analogue F<sub>6</sub>DiTAC<sub>11</sub> is endowed with longer polyTRIS branches. It is  
367 interesting to note that for an equivalent total number of TRIS units (18 for the two H<sub>8</sub>-  
368 DendriTACs and 21-22 for the two F<sub>6</sub>-DendriTACs), the impact of the “branching/elongation”  
369 effect is reversed between H<sub>8</sub>- and F<sub>6</sub>- chains. The aggregation behavior of F-DendriTACs

seems to be more affected by the branched geometry of the polar head groups ( $R_G$ - $R_H$  and  $N_{ag}$  decrease with the branching effect) compared to H-DendriTACs more affected by the elongation of polyTRIS units ( $R_G$ - $R_H$  and  $N_{ag}$  decrease with the elongation effect).

**Figure 5:** A, B, C represent respectively the structure (below) and proposed aggregation model (above) for  $G_1/AB_2$ ,  $G_1/AB_3$ , and  $G_2/AB_2$ - $AB_2$  amphiphiles



In regards to the F-DendriTACs series, they all possess the same  $C_6F_{13}C_2H_4$  hydrophobic chain length, either in a single or double-tail form. Always in agreement with the concept of packing parameter, for F-DendriTACs with rather identical heads in terms of the length and number of polyTRIS branches (comparing  $F_6DiTAC_7$  to  $DiF_6DiTAC_6$ ;  $F_6TriTAC_7$  to  $DiF_6TriTAC_8$  and  $F_6TetraTAC_6$  to  $DiF_6TetraTAC_6$ ), as the volume of the hydrophobic part increases (from single to double-tailed surfactants),  $P$  increases leading to larger objects (entries 7 & 11; 9 & 12; 10 & 13). In the same way, as for H-DendriTACs, the micelle size decreases with the addition of one polar branch, from  $AB_2$  to  $AB_3$  when polyTRIS branches have similar  $DP_n$  values (entries 7 & 9; 11 & 12, Figure 5-A&B).

In contrast, for a same hydrophobic tail and same branching structure, when the length of the headgroup increases from 7 to 11 TRIS units per branch (entries 7 & 8), both  $R_H$  and  $R_G$  slightly increases, whereas  $N_{ag}$  decreases. The decrease in  $N_{ag}$  can be explained by the fact that if the

headgroups are larger, less surfactants are required to fill the same volume. Indeed,  $N_{ag}$  is related to the geometric parameters of surfactants by the expression  $N_{ag} \sim (4\pi lo^2)/a_e$  (with  $a_e$  the equilibrium area per molecule at the aggregate surface and  $lo$  the tail length).<sup>33-35</sup> Thus, if  $a_e$  increases,  $N_{ag}$  decreases. However, we cannot rule out the possibility that the shape of micelles has changed as a result of the concept of molecular parameter (*vide supra*). Regarding the generations  $G_1$  and  $G_2$ , for F-DendriTACs with a same  $AB_2$  branching structure and close DPn value per polyTRIS branch,  $F_6DiTAC_7$  versus  $F_6TetraTAC_6$  and  $DiF_6DiTAC_6$  versus  $DiF_6TetraTAC_6$ , little variation in the size of the assemblies is observed ( $R_G$  and  $R_H$ ) although for the single-tailed (entries **7** & **10**)  $R_H$  slightly increases, while  $N_{ag}$  is divided by at least 2 (see entries **7** & **10**, **11** & **13**). This trend is consistent with the results described previously on the impact of the headgroup volume. Thus, between  $G_1$  and  $G_2$  series with identical apolar chains, the micelle shape is retained while  $G_2$  ones have a lower  $N_{ag}$  due to the wider/bulkier headgroup. Although there is no great variation in the size of the resulting assemblies, a difference in the transport properties may arise from  $G_1$  to  $G_2$  DendriTACs due to the volume variation of the central scaffold between polyTRIS branches (Figure 5-A&C).

For each single- or double-tail F-DendriTACs series of generation  $G_1$ , it is again noteworthy that the addition of a polyTRIS branch of similar length (entries **7** & **9**, **11** & **12**) leads to a decrease in micelle size. A decrease of the aggregation number is also observed as a consequence of the high curvature of the polar head group of each monomer engaged in the micelle.

**Comparison between H/F-surfactants.** It has long been shown for surfactants whose hydrophobic tail contains more than 6 perfluorinated carbons linked to a short hydrocarbonated part (methylene groups), that  $1\ CF_2 \approx 1.5-1.7\ CH_2$  ref.<sup>36, 37</sup> This means that a  $F_6$ -chain is equivalent to roughly a  $H_{10}$  one. In our case, since each perfluorocarbon tail is followed by two methylene units, the tail of the  $F_6$ -chain series is therefore equivalent to that of the  $H_{12}$ -chain



series, as confirmed by the size parameters for H- and F-DendriTACs, which have similar DP<sub>n</sub> values and same AB<sub>2</sub> branching type (see entries **3** & **7**). However, smaller assemblies are observed with fluorinated analogues due to the enhanced hydrophobic interaction and stiffness of the fluorocarbon chains that confers them a different packing into the micelle core compared to their hydrocarbon analogues. This is also observed for surfactants endowed with linear polar heads H- and F-TAC surfactants (see entries **14** & **15**). In both linear or dendritic families,  $N_{ag}$  is lower for F<sub>6</sub>-series than for H<sub>12</sub>-series due to the bulkiest and rigidity of F-chains that do not allow as much hydrophobic chains in the micelle core as for H-chains.

**Comparison between H/F-TAC and H/F-DendriTAC surfactants.** As mentioned above, H<sub>12</sub>TAC<sub>6</sub> and F<sub>6</sub>TAC<sub>7</sub> can be considered to have both comparable hydrophobic contribution of their tail and length of their polyTRIS polar head. However, smaller assemblies are obtained for F<sub>6</sub>TAC<sub>7</sub> due to the different molecular packing of fluorinated monomers into the supramolecular construct. Now, if we compare the linear surfactant F<sub>6</sub>TAC<sub>7</sub> to its closest dendritic counterpart F<sub>6</sub>DiTAC<sub>7</sub> it appears that the structural parameters of the resulting assemblies ( $R_G$ ,  $R_H$  and  $N_{ag}$ ) are very close. Then, if we extrapolate the comparison and consider F<sub>6</sub>TAC<sub>7</sub> as the AB<sub>1</sub> analogue of the F<sub>6</sub>-DendriTAC series, it seems that the presence of the central scaffold between the F<sub>6</sub>-chain and the polyTRIS head groups attenuates the impact of the branching effect on the micelle size and aggregation number when comparing F<sub>6</sub>TAC<sub>7</sub> (AB<sub>1</sub> analogue) to F<sub>6</sub>DiTAC<sub>7</sub> (AB<sub>2</sub> analogue). However, one can assume that the presence of the two triazole rings and the space between the two oligomeric head groups will influence their respective performances in terms of encapsulation efficiency or as potential nanoreactors. Addition of one supplementary polyTRIS branch to the polar head (from F<sub>6</sub>DiTAC<sub>7</sub> to F<sub>6</sub>TriTAC<sub>7</sub>) induces a decrease in the micelle size and aggregation number, as already commented (entries **7** & **9**). The same tendency is observed for double-tail analogues DiF<sub>6</sub>DiTAC<sub>6</sub> and DiF<sub>6</sub>TriTAC<sub>8</sub> (entries **11** & **12**). Surprisingly, the introduction of a fourth

polyTRIS branch *via* an increase in surfactant generation (from a  $G_1/AB_2$  polar head (entry 7) to a  $G_1/AB_3$  (entry 9) and then to a  $G_2/AB_2-AB_2$  *i.e.* a TetraTAC polar head (entry 10)) cancels out micelle size fluctuations without compensating for  $N_{ag}$  variations when moving from  $G_1/AB_2$  to  $G_1/AB_3$  and then to  $G_2/AB_2-AB_2$  monomers. The same trend can be seen with the double-tail surfactants (entries 11, 12 and 13, Figure 5-A, B & C). Again, we can assume that for comparable object size, these different types of assemblies will not offer the same loading capacity for drug delivery or as nanoreactors. For these application types, the high intrinsic variability of the self-assemblies generated by our new family of dendritic surfactants should make H/F-DendriTACs much more versatile platforms than H/F-TACs.

## CONCLUSION

In this study, the synthesis of a new dendritic surfactant family called H/F-DendriTAC is described, consisting of either hydrogenated or fluorinated alkyl chains grafted to dendronized hydrophilic oligomers leading to a high structural modularity. All compounds showed a good solubility in water, which allowed their self-assembling study. The aggregation behavior of fifteen surfactants was investigated using small-angle X-ray scattering (SAXS) and dynamic light scattering (DLS) to assess micellar structural parameters, such as their radius of gyration ( $R_G$ ), volume-weighted hydrodynamic radius ( $R_H$ ) and aggregation number ( $N_{ag}$ ). The versatility of the resulting molecular architectures (varying in both the nature, length and number of hydrophobic chains, and number and length of oligomeric polyTRIS polar branches) allows to obtain a large library of micellar aggregates of nanometric size and variable aggregation number. Overall, the high structural versatility of H/F-DendriTAC surfactants, which offers tunable self-assembly behaviors, opens perspectives for a wide range of applications. In ongoing researches, their potential use as nanoreactors for micellar catalysis and as nanocarriers for drug delivery will be investigated.

463

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