

# **CHEMISTRY** A European Journal



# Accepted Article

Title: Hexayne Amphiphiles and Bolaamphiphiles

Authors: Enzo Bomal, Vincent Croué, Reuben Jueyuan Yeo, Rosario Scopelliti, and Holger Frauenrath

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.201904890

Link to VoR: http://dx.doi.org/10.1002/chem.201904890

Supported by ACES



# Hexayne Amphiphiles and Bolaamphiphiles

Enzo Bomal, <sup>1</sup> Vincent Croué, <sup>1</sup> Reuben Yeo, <sup>1</sup>Rosario Scopelliti, <sup>2</sup> Holger Frauenrath<sup>1\*</sup>

<sup>1</sup> Ecole Polytechnique Fédérale de Lausanne (EPFL) Institute of Materials Laboratory of Macromolecular and Organic Materials

<sup>2</sup> Ecole Polytechnique Fédérale de Lausanne (EPFL) Institute of Chemical Sciences and Engineering (ISIC)

> EPFL–STI–IMX–LMOM MXG 135, Station 12 1015 Lausanne, Switzerland

> > Corresponding author:

holger.frauenrath@epfl.ch

This article is protected by copyright. All rights reserved.

# Abstract

Oligoynes with two or more conjugated carbon-carbon triple bonds are useful precursors for carbonrich nanomaterials. However, their range of appOlications has so far been severly limited by the challenging syntheses, particularly in the case of oligoynes with chemical functional groups. Here, we report a universal synthetic approach towards both symmetric and unsymmetric, functionalized hexaynes through the use of a modified Eglinton-Galbraith coupling and a sacrificial building block. We demonstrate the versatility of this approach by preparing hexaynes functionalized with phosphonic acid, carboxylic acid, ammonium, or thiol head groups, which serve as neutral, cationogenic, or anionogenic interfacially active groups. We show that these hexaynes are carbon-rich amphiphiles or bolaamphiphiles, that self-assemble at liquid-liquid interfaces, on solid surfaces, as well as in aqueous media.

Keywords: carbon-rich molecules, oligoynes, amphiphiles, surfactants, self-assembly

# Introduction

Molecules containing two or more conjugated carbon-carbon triple bonds are of interest for their use as precursors for polydiacetylenes<sup>[1,2]</sup> and carbon nanomaterials,<sup>[3-6]</sup> or as experimental models for carbyne, the fully sp-hybridized carbon allotrope.<sup>[7-10]</sup> For instance, diacetylenes in organized phases can undergo topochemical polymerization.<sup>[1],[11],[12]</sup> The resulting polydiacetylenes are conjugated polymers with unique optical properties as well as stimuli-responsive absorption and emission behavior that has been been implemented in one-dimensional self-assembled nanostructures,<sup>[13]</sup> monolayers,<sup>[14]</sup> or gels.<sup>[15]</sup> Some polydiacetylenes have also been investigated for their use as precursors of carbon-rich nanomaterials,<sup>[16],[17]</sup> including nanographenes,<sup>[18]</sup> as well as carbon fibers,<sup>[19]</sup> or graphene nanoribbons.<sup>[20],[21]</sup> One reason for the broad variety of structures and applications of diacetylenes and their polymers is the straightforward introduction of chemical functional groups, such as surface binding groups for monolayer formation,<sup>[22],[23]</sup> or amine and alcohol functions for further coupling reactions to more complex substituents. <sup>[13],[24]</sup>

Higher oligoyne homologues, such as triynes<sup>[25]</sup> or tetraynes,<sup>[26]</sup> have also been used to create carbon nanomaterials at carbonization temperatures of 800 °C, which is significantly lower than those required for other molecular precursors. Nevertheless, still milder conditions would be required to apply classical supramolecular self-assembly concepts to control the morphology of the produced carbon nanomaterials. It has been demonstrated that, starting from the hexaynes, the all-carbon segements are sufficiently reactive to allow complete carbonization to occur under conditions that are compatible with, for instance, colloidal or interfacial self-assembly.<sup>4,6</sup> In this way, carbon nanocapsules or carbon nanosheets have been obtained from vesicles in aqueous dispersions or from Langmuir-Blodgett films at the air-water interface, respectively.

The investigation of even longer oligoynes as a proxy towards the hypothetical carbon allotrope "carbyne" is synthetically more demanding due to the inherent instability of these oligoynes. To this end, sterically demanding side groups are typically employed to avoid the sp-hybridized carbons to come into reactive distance, such as triisopropylsilyl residues,<sup>[27]</sup> platinum complexes,<sup>[28,29]</sup> dendrons,<sup>[10]</sup> or various sterically demanding aryl groups,<sup>[30]</sup> notably including the supertrityl group.<sup>[7]</sup>

While the reasons for an interest in oligoyne synthesis may vary, the chemistry to access conjugated sphybridized segments is invariable and makes use of acetylene homocoupling and heterocoupling reactions. Typical homocoupling conditions, which are generally used to access higher oligoyne homologues, rely on mild oxidative coupling conditions, such as the Glaser-Hay coupling with oxygen catalyzed by a copper-TMEDA complex,<sup>[29,31,32]</sup> or the Eglinton-Galbraith protocol, which uses copper(II) acetate in the presence of a base.<sup>[7,33]</sup> These two coupling methods are robust and have been extensively used for the synthesis of higher oligoynes but only yield symmetric oligoyne molecules. In order to produce unsymmetric molecules, one needs to use heterocoupling reactions such as the Cadiot-Chodkiewicz coupling,<sup>[34]</sup> which is achieved by the condensation of a terminal alkyne with an alkynyl halide in the presence of copper(I) and an amine. While this method is widely applied in diacetylene synthesis, its use for higher oligoynes typically results in low conversions.<sup>[35,36]</sup> Alternative heterocoupling conditions include the Negishi protocol, which has been used to prepare functional hexaynes with however moderate yield.<sup>[6,35]</sup> Yin et al. recently employed Glaser-Hay conditions for the heterocoupling of alkynes. However, the selectivity for the heterocoupled product in these conditions is partly based on the acidity difference of two aromatic alkynes, which is not broadly applicable to other types of alkynes.<sup>[37]</sup> Tykwinski and coworkers extensively used the Fritsch-Buttenberg-Wiechell rearrangement in the synthesis of higher oligoynes,<sup>[27,32,38]</sup> which requires the use of a strong base that may prove to be problematic for the compatibility with functional oligoynes.



Figure 1. Structure of unsymmetric and symmetric hexayne molecules investigated in this work.

In marked contrast to the situation in diacetylene synthesis, functional higher oligoynes have rarely been reported in literature, with a few exceptions including a triyne carboxylic acid,<sup>[38]</sup> a tetrayne diol,<sup>[26]</sup> or the hexayne glucosides and carboxylates reported by our laboratory.<sup>[35]</sup> These difficulties of

introducing reactive or functional groups in a way compatible with the synthesis of the oligoyne segments severely limits their range of applications.

Here, we report the efficient preparation of the unsymmetric and symmetric hexaynes **1–7** bearing different kinds of functional groups for surface binding or interfacial activity, including phosphonic acid, carboxylic acid, amine, and thiol functions (Figure 1). The unsymmetric hexaynes **1–4** were accessed by a one-pot deprotection-coupling approach under Eglinton-Galbraith homocoupling conditions using a sacrificial triyne building block, while the symmetric hexaynes **5–7** were straightforwardly obtained following the same protocol without the sacrificial triyne. This approach increased the isolated yield of the functional hexaynes by a factor of nine compared to the synthesis via a Negishi coupling reaction. In this way, we were able to prepare interfacially active carbon-rich amphiphiles or bolaamphiphiles with anionogenic, cationogenic, or neutral head groups that can stabilize the liquid-liquid interface, form self-assembled monolayers on inorganic solid surfaces, or undergo colloidal self-assembly in aqueous media.

### **Results and Discussion**

In order to limit the degradation of the highly reactive hexayne segment as far as possible, we decided to synthesize it following a convergent approach based on the coupling of two triynes in the last step. Both the symmetric and the unsymmetric hexaynes were obtained using a modified Eglinton-Galbraith coupling protocol,<sup>[36]</sup> either using it for a homocoupling of the corresponding triynes in the case of **5–7**, or by performing a statistical heterocoupling employing an excess of the alkyl-terminated 1-trimethylsilyloctadeca-1,3,5-triyne in the case of **1–4**.<sup>[39,40]</sup>

This synthetic approach allowed us to prepare the hexayne phosphonic acid **1** in five steps (Scheme 1). We first subjected 6-iodo-1-hexyne **8** to a Michaelis-Becker reaction<sup>[41]</sup> with diethyl phosphite, which furnished 5-hexyne phosphonic acid diethyl ester **9** in 83% yield. Bromination of the terminal alkyne with *N*-bromosuccinimide (NBS) and AgNO<sub>3</sub> gave 6-bromo-5-hexyne phosphonic acid diethyl ester **10** in 90% yield. A subsequent Negishi coupling reaction with 1,4-bis(trimethylsilyl)buta-1,3-diyne resulted in the trimethylsilyl-protected triyne **11** in 77% yield, which confirmed the robustness of the Negishi coupling reaction for triyne synthesis.<sup>[39,40]</sup> The triyne **11** was again converted to the corresponding bromotriyne **12** by bromination with NBS/AgF that was obtained in 72% yield after purification by column chromatography (Scheme 1).



**Scheme 1.** Synthesis of the hexayne phosphonate **13**. *Reagents and conditions*: *a*) HPO<sub>3</sub>Et<sub>2</sub>, NaHMDS, THF, r.t., 16 h, 83%; *b*) NBS, AgNO<sub>3</sub>, DCM/MeCN, r.t., 4 h, 90%; *c*) MeLi · LiBr, ZnCl<sub>2</sub>, Pd(dppf)Cl<sub>2</sub> · DCM, 1,4-bis(trimethylsilyl)butadiyne, THF/toluene, 0 °C, 24 h, 77%; *d*) NBS, AgF, DCM/MeCN, r.t., 4 h, 72%; *e*) MeLi · LiBr, ZnCl<sub>2</sub>, Pd(dppf)Cl<sub>2</sub> · DCM, 1-trimethylsilyloctadeca-1,3,5-triyne, THF/toluene, 0 °C, 24 h, 10%.



**Scheme 2.** Synthesis of the hexayne phosphonic acids **1** and **5**. *Reagents and conditions*: *a*) CsF, Cu(OAc)<sub>2</sub>, 1-trimethylsilyloctadeca-1,3,5-triyne, DCM/MeOH/2,6-lutidine, r.t., 16 h, 67%; *b*) CsF, Cu(OAc)<sub>2</sub>, DCM/MeOH/2,6-lutidine, r.t., 16 h, 94%; *c*) TMS–Br, DCM, r.t., 3 h, 48%; *d*) TMS–Br, DCM, r.t., 3 h, 60%.

We initially intended to subject this bromotriyne **12** to another Negishi coupling with 1trimethylsilyloctadeca-1,3,5-triyne in order to prepare the hexayne phosphonate **13** (Scheme 1), by analogy to other hexayne syntheses reported previously by our group. However, the yield of **13** never exceeded 10% after column chromatography following this procedure with various modifications, which severely limits the applicability of such functional hexayne derivatives. This negative finding confounds our observations that the Negishi coupling protocol worked well in triyne synthesis, even in the presence of polar functional groups, but only works reliably for the coupling of two triynes if both of them are equipped with sterically demanding terminal groups.<sup>[6],[35]</sup> Since the hexayne product itself appeared to be stable at room temperature over weeks in solution, we hypothesized that unstable intermediates in the Negishi coupling reaction were the root of the problem, and not the stability of the product itself.

We therefore devised an alternative route (Scheme 2), making use of homocoupling conditions and employing one of the two triynes as a sacrificial component in large excess (5 equiv.). We decided to use 1-trimethylsilyloctadeca-1,3,5-triyne as the sacrificial component, because it can be straightforwardly synthesized on a 30 g scale, and because it is the common component used in the synthesis of the four unsymmetric functional hexaynes **1–4**. Our choice for the coupling conditions was inspired by the modified Eglinton-Galbraith homocoupling developed by Twikinski et al,<sup>[7]</sup> which removes the trimethyl silyl group *in situ* and uses the more sterically demanding 2,6-lutidine instead of pyridine as the base. We considered this to be advantageous because the resulting hexaynes are known to be sensitive to nucleophiles. For the coupling of the 1-trimethylsilyloctadeca-1,3,5-triyne to the trimethylsilyl-protected triyne **11**, the cleavage of the trimethyl silyl groups for both triynes was first performed *in situ* by the addition of CsF, before starting the coupling by the addition of copper acetate. Using this one-pot procedure, diethyl octacosa-5,7,9,11,13,15-hexayn-1-ylphosphonate **13** was obtained in a yield of 67%, which represents a nine-fold increase in yield in comparison to the Negishi coupling approach.

The final cleavage of the phosphonate ester groups is another critical step in the synthesis of the hexayne phosphonic acid amphiphile **1** (Scheme 2). The hexayne itself is sensitive to light, heat, and alkaline conditions, which severely limits the options for a removal of protective groups. We finally successfully cleaved the phosphonate esters using trimethylsilyl bromide (TMS–Br) at room temperature. The product was purified by precipitation upon the addition of 1 M HCl solution, furnishing octacosa-5,7,9,11,13,15-hexayn-1-yl phosphonic acid **1** as a yellow solid (67%). The overall yield for the synthesis of the unsymmetric hexayne amphiphile was hence 23% over five steps. The product was stable in dilute solution (DCM/MeOH 3:1, *c* = 0.2 mmol/L) at room temperature over several weeks, and was therefore kept in stock solutions for long-term storage.

Conveniently, the same approach can be applied to prepare the symmetric hexayne diphosphonic acid **5** (Scheme 2). To this end, the triyne **11** was subjected to the in-situ deprotection and the modified

Eglinton-Galbraith homocoupling reaction without the use of a second component, furnishing the hexayne **14** as a yellow crystalline solid in a yield of 94%. The phosphonic esters in **14** were finally cleaved using TMS–Br, and the hexayne diphosphonic acid **5** was obtained as a yellow solid in a yield of 48%. The compound was stable in dilute solution (DCM/MeOH 1:1, c = 0.2 mmol/L) at room temperature over several weeks and kept in stock solutions for long-term storage.



**Scheme 3.** Synthesis of the triyne *tert*-butyl ester **18**. *Reagents and conditions*: *a*) trifluoroacetic anhydride, <sup>t</sup>BuOH, THF, 0 °C, 16 h, 63%; *b*) NBS, AgNO<sub>3</sub>, DCM/MeCN, r.t., 4 h, 63%; *c*) MeLi · LiBr, ZnCl<sub>2</sub>, Pd(dppf)Cl<sub>2</sub> · DCM, 1,4-bis(trimethylsilyl)butadiyne, THF/toluene, 0 °C, 72 h, 90%.



**Scheme 4.** Synthesis of the hexayne carboxylic acids **2** and **6**. *Reagents and conditions: a)* CsF, Cu(OAc)<sub>2</sub> 1-trimethylsilyloctadeca-1,3,5-triyne, DCM/MeOH/2,6-lutidine, r.t., 14 h, 46%; *b*) CsF, Cu(OAc)<sub>2</sub>, DCM/MeOH/2,6-lutidine, r.t., 14 h, 66%; *c*) trifluoroacetic acid (TFA), DCM, r.t., 1 h, 68%; *d*) TFA, DCM, r.t., 1 h, 59%.

We turned to synthesizing the corresponding unsymmetric hexayne carboxylic acid **2** and the symmetric hexayne dicarboxylic acid **6** using the the same approach (Scheme 3 and 4). However, it was necessary to find a suitable protecting group. We had used the triphenylphenyl ester function in

previous work,<sup>[6]</sup> but its cleavage in basic conditions typically results in the degradation of considerable quantities of the hexaynes, demonstrating their sensitivity to bases and nucleophiles. Therefore, we decided to use the *tert*-butyl ester derivatives instead, as they are sterically demanding and can be cleaved in mild acidic conditions.

After protection of the hex-5-ynoic acid 15 using tert-butanol and trifluoroacetic anhydride, the resulting hexynoyl *tert*-butyl ester **16** was brominated to give *tert*-butyl 6-bromohex-5-ynoate **17** in 63% yield after column chromatography (Scheme 3). The brominated alkyne 17 was subjected to a Negishi coupling 1,4-bis(trimethylsilyl)buta-1,3-diyne, furnishing *tert*-butyl 10with (trimethylsilyl)deca-5,7,9-triynoate **18** as a brown oil in 90% yield. The subsequent *in-situ* desilylation and Eglinton-Galbraith coupling with an excess of 1-trimethylsilyloctadeca-1,3,5-triyne then resulted in the desired *tert*-butyl octacosa-5,7,9,11,13,15-hexaynoate 19, which was isolated as a yellow solid in a yield of 46% after purification by silica gel column chromatography (Scheme 4). Finally, the cleavage of the *tert*-butyl ester protecting group was achieved by treating the protected hexayne **19** with a solution of trifluoroacetic acid (TFA) in DCM (1:4), resulting in the free octacosa-5,7,9,11,13,15-hexaynoic acid 2 as a pale yellow powder in a yield of 68% that was stored in solution (DCM, c = 1.0 mmol/L) to avoid degradation.

The symmetric hexayne dicarboxylic acid was obtained using a Eglinton-Galbraith homocoupling of triyne **18** in 66% yield (Scheme 4). The product was recrystallized from a mixture of DCM and pentane, resulting in yellow single crystals suitable for X-ray structure analysis (see below). The free icosa-5,7,9,11,13,15-hexaynedioic acid **6** was finally prepared by cleavage of the *tert*-butyl ester group in TFA/DCM (1:4) and obtained in 59% yield as a yellow powder that was soluble in alkaline aqueous solution (sat. NaHCO<sub>3</sub>). The final product was kept in solution for long term storage (DCM/MeOH 1:3, *c* = 3.0 mmol/L).

The corresponding amino-functional hexaynes were prepared using a similar strategy (Scheme 5 and 6). The *tert*-butyl carbamate (Boc) protecting group was selected for its steric demand and its convenient cleavage in mild acidic conditions. To this end, *N*-Boc-5-aminopentyne was prepared from 5-hexyne carboxylic acid by a one-pot Curtius rearrangement and Boc-protection procedure, analogous to the report by Selvam and coworkers.<sup>[42]</sup> The product was obtained in 25% yield after column chromatography in DCM. The terminal alkyne was brominated with NBS/AgNO<sub>3</sub> to give **22** in 92% yield. The subsequent Negishi coupling to 1,4-bis(trimethylsilyl)butadiyne resulted in the Boc-protected

amino-terminated triyne **23** in 84% yield after column chromography in DCM (Scheme 5). This triyne was then used in the *in-situ* desilylation and Eglinton-Galbraith coupling with an excess of 1-trimethylsilyloctadeca-1,3,5-triyne as a sacrificial component, to give *N*-Boc-heptacosa-4,6,8,10,12,14-hexaynamine **24** as a yellow powder in 53% yield. The final cleavage of the Boc protecting group was achieved using a mixture of 4 M HCl in dioxane and DCM, and the product was precipitated by the addition of large volume of DCM to the reaction mixture. The precipitate was thoroughly washed with pure DCM, to give the unsymmetric heptacosa-4,6,8,10,12,14-hexayne ammonium chloride **3** as a yellow powder in 74% yield, before being redissolved in a DCM/MeOH mixture (1:1, *c* = 1.1 mmol/L) for long-term storage (Scheme 6).



**Scheme 5.** Synthesis of the protected aminotriyne **23**. *Reagents and conditions: a*) propylphosphonic anhydride, <sup>t</sup>BuOH, NaN<sub>3</sub>, tetrabutylammonium bromide (TBAB), NEt<sub>3</sub>, THF, 4 h, 25%; *b*) NBS, AgNO<sub>3</sub>, DCM/MeCN, r.t., 3 h, 92%; *c*) MeLi · LiBr, ZnCl<sub>2</sub>, Pd(dppf)Cl<sub>2</sub> · DCM, 1,4-bis(trimethylsilyl)butadiyne, THF/toluene, 0 °C, 48 h, 84%.



**Scheme 6.** Synthesis of the amino-functional hexaynes **3** and **7**. *Reagents and conditions: a*) CsF, Cu(OAc)<sub>2</sub>, 1-trimethylsilyloctadeca-1,3,5-triyne, DCM/MeOH/2,6-lutidine, r.t., 14 h, 53%; *b*) CsF, Cu(OAc)<sub>2</sub>, DCM/MeOH/2,6-lutidine, r.t., 14 h, 66%; *c*) 4 M HCl in dioxane/DCM, r.t., 2 h, 74%; *d*) 2 M HCl, DCM/dioxane, r.t., 2 h, 99%.

The symmetric hexayne diamine was obtained by a Eglinton-Galbraith homocoupling of the Bocprotected amino-terminated triyne **23**, giving the symmetric Boc-protected hexayne diamine **25** as a yellow solid in 66% yield (Scheme 6). Recrystallization of the product, using similar conditions as for the symmetric phosphonate diester hexayne **20** and symmetric *tert*-butyl ester hexayne **14**, yielded yellow, but very thin, needle-like crystals unsuitable for X-Ray diffraction analysis. The final cleavage of the Boc groups was achieved using a mixture of 4 M HCl in dioxane and DCM. Precipitation by the addition of DCM resulted in the symmetric octadeca-4,6,8,10,12,14-hexayne diammonium chloride **7**, which was obtained in 99% yield as yellow powder, showing good solubility in aqueous 1 M HCl solution (Scheme 6). The molecule was kept in a MeOH solution (1.5 mmol/L) for long term storage.



**Scheme 7.** Synthesis of the triyne active ester **28**. *Reagents and conditions: a*) 2,3,5,6-tetrafluorophenol, DCC, DMAP, DCM, r.t., 24 h, quant.; *b*) AgNO<sub>3</sub>, NBS, DCM/MeCN, r.t., 4 h, 85%; *c*) MeLi · LiBr, ZnCl<sub>2</sub>, Pd(dppf)Cl<sub>2</sub> · DCM, 1,4-bis(trimethylsilyl)butadiyne, THF/toluene, 0 °C, 24 h, 65%.



**Scheme 8.** Synthesis of the hexayne thiol **4**. *Reagents and conditions: a*) 2-aminoethyl thioacetate, diisopropylethylamine (DIPEA), DCM, r.t., 16 h, 38%; *b*) 2-aminoethyl trityl thioether, DIEPA, DCM, r.t., 16 h, 76%; *c*) CsF, Cu(OAc)<sub>2</sub>, 1-trimethylsilyloctadeca-1,3,5-triyne, DCM/MeOH/2,6-lutidine, r.t., 16 h; *d*) CsF, Cu(OAc)<sub>2</sub>, 1-trimethylsilyloctadeca-1,3,5-triyne, DCM/MeOH/2,6-utidine, r.t., 16 h, 48%; *e*) TFA/DCM 1:1, phenol (2.5 *wt*%), r.t., 2 h.

The introduction of thiol functions in hexaynes turned out to be less straightforward. After several attempts with various protected thiol derivatives, it became clear that their presence was incompatible with the Negishi coupling protocol used for the synthesis of the triyne precursors, supposedly due to poisoning of the Pd catalyst. We therefore decided to first synthesize a corresponding active ester derivative, and subsequently introduce the thiol by reaction with a protected aminoethanethiol derivative (Scheme 7 and 8).

The reaction of hex-5-ynoic acid **15** with 2,3,5,6-tetrafluorophenol using *N*,*N*'-dicylcohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as the coupling reagents furnished 2,3,5,6-tetrafluorophenyl hex-6-ynoic ester **26** in quantitative yield.<sup>[43]</sup> The hexyne **26** was brominated with NBS/AgNO<sub>3</sub> to give the corresponding bromohexyne **27** in 85% yield (Scheme 7). This compound was subjected to a Negishi coupling reaction to 1,4-bis(trimethylsilyl)butadiyne to prepare the triyne active ester **28** in 65% yield after column chromatography. At this point, the active ester was converted to an amide by treatment with 2-aminoethyl thioacetate in presence of diisopropylethylamine (DIPEA) as the base, to form triyne thioacetate **29** in 38% yield (Scheme 8). Compound **29** was then subjected to the

Eglinton-Galbraith coupling using an excess of 1-trimethylsilyloctadeca-1,3,5-triyne as a sacrificial component. However, this reaction resulted in a mixture of a low amount of the desired hexayne thioacetate **30a**, as well as compound **30b** as a major side product. The formation of this side product may be explained by a cleavage of the thioacetate in the basic reaction medium followed by a Cu(I)-catalyzed oxidative coupling of the triyne and the free thiol, similar to a reaction reported in the literature.<sup>[44]</sup> To avoid the premature deprotection of the thiol and the formation of undesired side products, we decided to proceed with tritylthioether **31** instead, which was prepared by a reaction of the active ester **28** with 2-aminoethyl trityl thioether in a yield of 76%. Eglinton-Galbraith coupling of compound **31** to 1-trimethylsilyloctadeca-1,3,5-triyne furnished the hexayne tritylthiol **32** as a yellow solid in 48% yield after silica gel column chromatography in DCM. Finally, the hexayne was deprotected by stirring in a solution of TFA/DCM (1:1) using phenol (2.5 *wt*%) as a cation scavenger. The hexayne thiol **4** was purified by column chromatography (EtOAc/pentane, 1:1) and had to be kept in solution to avoid rapid degradation (Scheme 8).

# Crystal Structure Analysis

Single crystals of the symmetric hexayne diethylphosphonate **14** and the symmetric hexayne *tert*-butyl carboxylate **20** suitable for X-ray crystal structure analysis were obtained by the slow evaporation at  $-15^{\circ}$ C of solutions in DCM/pentane (1:2) and DCM/hexane (1:1), respectively (*c* = 5 mg/mL).

Compounds **14** and **20** both crystallized in the space group *P*-1 with the lattice parameters *a* = 8.0518 Å, *b* = 9.3492 Å, *c* = 19.979 Å,  $\alpha$  = 84.13°,  $\beta$  = 89.695°, and  $\gamma$  = 73.631° (Figure 2a,b) and *a* = 5.8314 Å, *b* = 11.4602 Å, *c* = 19.009 Å,  $\alpha$  = 105.16°,  $\beta$  = 93.979°, and  $\gamma$  = 90.702° (Figure 2c,d), respectively (Figure 2). The crystal packing of compound **14** and **20** were both characterized by layers of the molecules parallel to the crystallographic *ab* planes. Within these layers, the molecules were arranged into pairs, held together by C–H···O=P short contacts and C–H···O=C short contacts, respectively. The pairs of molecules formed stacks along the crystallographic *b* axis in both cases.

The hexayne segment in compound **14** was essentially linear, with bond angles around acetylenic carbons of 177.3(5)–179.8(6)°, and showed a slight bond length alternation, with average bond lengths of 1.216(6) Å for the six carbon-carbon triple bonds and 1.354(6) Å for the five internal carbon-carbon single bonds, very similar to the structural features of other oligoynes in the crystalline state.<sup>[32,45]</sup>



**Figure 2.** Crystal structures of *a*,*b*) the hexayne diphosphonate **14** and *c*,*d*) the hexayne dicarboxylate **20**, including carbon-carbon short contacts between the hexayne segments.

Likewise, the hexayne segment of molecule **20** showed a slight bond length alternation with average bond lengths of 1.200(7) and 1.360(7) Å for the triple and single bonds, respectively, and was almost linear, with bond angles in the range of 177.8(6)–179.5(5)°. The last two carbons at one end of the hexayne (C11 and C12) as well as the adjacent spacer (C21, C22, C23) exhibited a large degree of disorder, which we suspected to be is due to partial crosslinking.

Within the molecular stacks of the hexayne diphosphonate **14**, neighboring hexayne segments exhibited  $\pi$ - $\pi$  interactions with carbon-carbon short contacts between carbons 1, 3, and 5 of one molecule with carbons 8, 10, and 12 of its neighbor, respectively (Figure 2a,b), of which the shortest is C(3)…C(10) with 3.467(6) Å. These short contacts are hence well below the reactive distance of 4 Å, and the *b* axis parameter would be appropriate for a 1,8-topochemical tetrayne polymerization. In the case of the hexayne dicarboxylate **20**, the shortest hexayne to hexayne contact is C(3)…C(5) with 3.482(6), and numerous other short contacts below 4 Å exist (Figure 2c,d), which indicate the possibility for topochemical polymerization along the crystallographic *b* axis. When left at room temperature for several minutes, both compounds turned brown and showed signs of uncontrolled crosslinking, as indicated by the degrading X-ray diffraction results. An attempt to crosslink the crystals under UV-

irradiation at 0°C yielded a brown oil after 1 h of irradiation, once again indicative of an ill-defined crosslinking process leading to the destruction of the crystal structure.

#### Molecular and Interfacial Characterization

The solution-phase UV-Vis spectra of all surfactants showed the typical absorption peaks of the hexayne chromophore (Figure 3a) with the main absorption peak in the UV region and the presence of the characteristic vibronic fine structure of hexaynes. The absorption spectra of the unsymmetric hexaynes 1-4 in dichloromethane exhibited a main optical absorption at 293 nm, and further absorptions at 277 and 263 nm. The UV-Vis spectra of the symmetric hexaynes 5-7 in isopropyl alcohol showed absorptions at 289, 273, and 258 nm, with the 4 nm blue shift compared to **1–4** supposedly due to a solvatochromic effect. The main optical absorptions, however, do not correspond to the lowest-lying transition that is forbidden due to the symmetry of the hexayne chromophore, but has been assigned to a  $S_0 \rightarrow S_n$  absorption.<sup>[46]</sup> However, in the case of the unsymmetric surfactants **1**, **2** and **4**, the lower molecular symmetry renders the otherwise forbidden transition  $S_0 \rightarrow S_{2/3}$  with absorptions at at 314 and 334 nm weakly allowed. In the case of compound **3**, the unsymmetric substitution combined with the positively charged ammonium group apparently even renders the otherwise dipole-forbidden  $S_0 \rightarrow S_1$ transition weakly allowed, as evident from the additional absorption bands at 399, 429 and 464 nm. By contrast, the symmetric hexaynes **5** and **6** did not show any significant other absorption than the main hexayne peaks, while some weak absorptions at 317 nm and 339 nm were observed for the symmetric hexayne diamine 7.



**Figure 3.** Molecular and interfacial characterization of hexayne amphiphiles. a) UV-Vis spectra of **1–7**, (**1–4** in DCM, **5–7** in IPA) showed the main optical absorptions below 300 nm typical of hexaynes chromophores, as well as weaker bands attributed to otherwise forbidden transitions.<sup>[46]</sup> b) Representative contact angle measurements of gold and aluminium oxide substrates before and after immersion in solutions of hexaynes **1–7**. c) Interfacial tension measurements of solutions of hexaynes **1–7** at the chloroform-water interface. d) Representative examples of the DLS size distribution by intensity of self-assembled unsymmetric hexayne **1–3**, showing one population of aggregates for compounds **2** and **3**, and two populations of aggregate for compound **1**. e) UV-Vis spectra of **1–3** in THF and after self-assembly in water after subtraction of the scattering background (see Supplementary Figure S1 for more information).

In order to investigate the surfactant properties of the functional hexaynes **1–7** at the solid-liquid interface, aluminium oxide substrates were immersed in solutions of the phosphonic acids **1** and **5** (isopropyl alcohol, c = 0.2 mmol/L, 48 h) or the carboxylic acids **2** and **6** (toluene/isopropyl alcohol 1:1, c = 1 mmol/L, 72 h), while gold substrates were used for solutions of the hexayne thiol **4** (ethanol, c = 1 mmol/L, 24 h). From contact angle measurements of the immersed samples, one can conclude that, all hexaynes formed self-assembled monolayers of varying degrees of order on the appropriate

substrates (Figure 3b, Table 1). The hexayne thiol **7** on gold exhibited a contact angle of 107°, similar to the contact angles of around 108–110° observed for the crystalline self-assembled monolayers of octadecyl phosphonic acid on aluminum oxide or octadectanethiol on gold.<sup>[47]</sup> The hexayne phosphonic acid **1** exhibited a slightly lower contact angle of about 104°, which is indicative of a less well-ordered packing comprising *gauche*-defects in the molecular conformations. The even lower contact angles of both the hexayne carboxylic acid **2** and octadecanoic acid suggest the formation of increasingly defectrich monolayers. The contact angles observed for the hexayne bolaamphiphiles **5** and **6** indicate the presence of loop structures that prevent a full surface coverage and expose the hydrophobic segment.<sup>[48],[49]</sup> Thus, we conclude that the hexaynes **1–7** behave similar to the corresponding alkyl surfactants and that particularly the unsymmetric hexayne amphiphiles **1–4** display surface activity.

Table 1. Water contact angles of bare substrates and coated substrates, including a comparison of hexayne surfactant with a
pure alkyl surfactant.

Surface	Substrate	Water Contact Angle
bare Al <sub>2</sub> O <sub>3</sub>	Al <sub>2</sub> O <sub>3</sub>	26.8 ± 1.5
bare gold	Au	$86.0 \pm 2.0$
PO <sub>3</sub> H <sub>2</sub> -C <sub>4</sub> H <sub>8</sub> -C <sub>12</sub> -C <sub>12</sub> H <sub>25</sub> (1)	Al <sub>2</sub> O <sub>3</sub>	$104.4 \pm 0.7$
COOH-C <sub>3</sub> H <sub>6</sub> -C <sub>12</sub> -C <sub>12</sub> H <sub>25</sub> (2)	$Al_2O_3$	$102.0 \pm 0.5$
SH-C <sub>6</sub> H <sub>11</sub> NO-C <sub>12</sub> -C <sub>12</sub> H <sub>25</sub> (4)	Au	$107.2 \pm 0.7$
PO <sub>3</sub> H <sub>2</sub> -C <sub>4</sub> H <sub>8</sub> -C <sub>12</sub> -C <sub>4</sub> H <sub>8</sub> -PO <sub>3</sub> H <sub>2</sub> <b>(5)</b>	Al <sub>2</sub> O <sub>3</sub>	$86.6 \pm 0.4$
COOH-C <sub>3</sub> H <sub>6</sub> -C <sub>12</sub> -C <sub>3</sub> H <sub>6</sub> -COOH <b>(6)</b>	Al <sub>2</sub> O <sub>3</sub>	$73.4 \pm 0.6$
PO <sub>3</sub> H <sub>2</sub> -C <sub>18</sub> H <sub>37</sub>	Al <sub>2</sub> O <sub>3</sub>	110.3 ±1.2
COOH-C <sub>18</sub> H <sub>37</sub>	Al <sub>2</sub> O <sub>3</sub>	97.6 ± 0.7
SH-C <sub>18</sub> H <sub>37</sub>	Au	$108.4 \pm 1.0$
$PO_{3}H_{2}$ - $C_{12}H_{24}$ - $PO_{3}H_{2}$	Al <sub>2</sub> O <sub>3</sub>	85.3 ± 0.3
COOH-C <sub>10</sub> H <sub>20</sub> -COOH	$Al_2O_3$	83.8 ± 1.0

Next, we investigated the interfacial activity of the hexayne amphiphiles **1–7** by means of drop tensiometry at the chloroform/water interface (Figure 3c). To this end, the hexayne amphiphiles **1–4** were dissolved in the chloroform phase, and a pendant drop was formed in a water phase. The bolaamphiphiles **5–7** were dissolved in aqueous media adjusted to pH 13 (**5** and **6**) or pH 3 (**7**), and an inverted pendant drop was formed in a chloroform phase. The significantly reduced interfacial tensions proved that the unsymmetric hexaynes **1–3** stabilized the chloroform/water interface, while the neutral hexayne mercaptane **4** as well as the symmetric hexayne bolaamaphiphiles **5–7** did not show a strong interfacial affinity for the chloroform/water interface, in spite of their bolaamphiphilic molecular structure.

Since the unsymmetric hexayne amphiphiles **1–3** showed strong interfacial activity, we finally investigated their self-assembly in aqueous media upon dissolution of 0.5 mL of a stock solution in THF ( $c = 1 \mod/L$ ) with 5 mL of deionized water. Analysis of the obtained, visually transparent colloidal dispersions by dynamic light scattering (DLS) proved that the hexayne amphiphiles **2** and **3** gave rise to objects with hydrodynamic radii ( $R_h$ ) of 167±6 nm (PDI = 0.21) and 113±2 nm (PDI = 0.13), respectively, suggesting the formation of vesicular aggregates. The DLS results of the slightly turbid hexayne phosphonic acid **1** aqueous solution showed two populations, with peak means of 119±65 nm and 750±84 nm, which suggested that, in addition to vesicular aggregates similar to those observed for **2** and **3**, larger colloidal structures were formed. Finally, the UV-Vis spectra of the colloidal dispersions of hexaynes **1–3** in aqueous media exhibited intense scattering (Figure 3d,e, Supplementary Figure S1). The strongly reduced intensity ratio of the first and second vibronic bands at 277 nm and 293 nm, especially in the case of the compound **2** and **3**, can be explained with the formation of spectroscopic H-aggregates in the colloidal aggregates, indicating that the hexayne chromophores are closely packed in a predominantly cofacial arrangement in the colloidal aggregates. Nevertheless, the clearly visible hexayne absorptions show that no significant crosslinking occurred in the aggregated state .

#### Conclusions

We successfully prepared seven different hexayne amphiphiles, bearing neutral, cationogenic, or anionogenic head groups. Our synthetic approach relied on the preparation of the corresponding functionalized trivenes by a Negishi coupling reaction, followed by the preparation of the final hexaynes by a modified Eglinton-Galbraith coupling protocol. The latter was, on one side, implemented as a homocoupling reaction to produce symmetric hexayne bolaamphiphiles **5–7**, while it was also successfully applied as a heterocoupling reaction for the preparation of the unsymmetric hexayne amphiphiles **1–4** using an excess of an alkyl triyne as a sacrificial component. It turned out to be important to choose protecting groups for the different functional groups that were sterically demanding and could be cleaved in the final step in mild neutral or acidic conditions, while avoiding nucleophiles, bases, or the application of heat. In this way, we obtained the hexayne amphiphiles **1–7** in overall yields of 8–23% over 4–6 steps starting from commercial precursors. All compounds behaved as surfactants that formed self-assembled monolayers from organic solutions on appropriate solid surfaces, while only the ionogenic unsymmetric hexayne amphiphiles **1–3** exhibited interfacial activity at liquid-liquid (oil-water) interfaces. These hexayne amphiphiles were further shown to form vesicular aggregates in aqueous dispersions. Having in hand these hexayne surfactants and amphiphiles thus opens new opportunities to explore their use as precursors for the preparation of carbon-rich nanomaterials at liquid-liquid or liquid-solid interfaces, including carbon nanomembranes, nanocapsules, or nanocoatings.

#### Acknowledgments

Dr. Bjoern Schulte is gratefully acknowledged for preliminary investigations relevant to this manuscript. This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement no. 665667.

#### References

- [1] R. Xu, V. Gramlich, H. Frauenrath, J. Am. Chem. Soc. **2006**, *128*, 5541–5547.
- [2] E. Jahnke, J. Weiss, S. Neuhaus, T. N. Hoheisel, H. Frauenrath, *Chemistry A European Journal* **2009**, *15*, 388–404.
- [3] T. N. Hoheisel, S. Schrettl, R. Szilluweit, H. Frauenrath, *Angewandte Chemie International Edition* **2010**, *49*, 6496–6515.
- [4] R. Szilluweit, T. N. Hoheisel, M. Fritzsche, B. Ketterer, A. Fontcuberta i Morral, D. Demurtas, V. Laporte, R. Verel, S. Bolisetty, R. Mezzenga, et al., *Nano Lett.* **2012**, *12*, 2573–2578.
- [5] S. Schrettl, H. Frauenrath, *Angewandte Chemie International Edition* **2012**, *51*, 6569–6571.
- [6] S. Schrettl, C. Stefaniu, C. Schwieger, G. Pasche, E. Oveisi, Y. Fontana, A. F. I. Morral, J. Reguera, R. Petraglia, C. Corminboeuf, et al., *Nature Chemistry* **2014**, *6*, 468–476.
- [7] W. A. Chalifoux, R. R. Tykwinski, *Nature Chemistry* **2010**, *2*, 967–971.
- [8] S. Eisler, A. D. Slepkov, E. Elliott, T. Luu, R. McDonald, F. A. Hegmann, R. R. Tykwinski, *J. Am. Chem. Soc.* **2005**, *127*, 2666–2676.
- [9] T. R. R, C. Wesley, E. Sara, L. Andrea, T. Matteo, F. Daniele, Del Zoppo Mirella, Z. Giuseppe, *pac* **2010**, *82*, 891.
- [10] T. Gibtner, F. Hampel, J.-P. Gisselbrecht, A. Hirsch, *Chemistry A European Journal* **2002**, *8*, 408–432.
- [11] G. Wegner, *Naturforsch* **1969**, *24*, 824–832.
- [12] D. N. Batchelder, S. D. Evans, T. L. Freeman, L. Haeussling, H. Ringsdorf, H. Wolf, *J. Am. Chem. Soc.* **1994**, *116*, 1050–1053.

- [13] E. Jahnke, J. Weiss, S. Neuhaus, T. N. Hoheisel, H. Frauenrath, *Chemistry A European Journal* **2009**, *15*, 388–404.
- [14] D. Day, H. Ringsdorf, Journal of Polymer Science: Polymer Letters Edition **1978**, *16*, 205–210.
- [15] E. Jahnke, I. Lieberwirth, N. Severin, J. P. Rabe, H. Frauenrath, *Angewandte Chemie International Edition* **2006**, *45*, 5383–5386.
- [16] M. N. Tahir, A. Nyayachavadi, J.-F. Morin, S. Rondeau-Gagné, *Polym. Chem.* **2018**, *9*, 3019–3028.
- [17] A. Sun, J. W. Lauher, N. S. Goroff, *Science* **2006**, *312*, 1030.
- [18] W. Yang, R. Bam, V. J. Catalano, W. A. Chalifoux, *Angewandte Chemie International Edition* **2018**, *57*, 14773–14777.
- [19] L. Luo, D. Resch, C. Wilhelm, C. N. Young, G. P. Halada, R. J. Gambino, C. P. Grey, N. S. Goroff, *J. Am. Chem. Soc.* **2011**, *133*, 19274–19277.
- [20] R. S. Jordan, Y. L. Li, C.-W. Lin, R. D. McCurdy, J. B. Lin, J. L. Brosmer, K. L. Marsh, S. I. Khan, K. N. Houk, R. B. Kaner, et al., *J. Am. Chem. Soc.* 2017, *139*, 15878–15890.
- [21] R. S. Jordan, Y. Wang, R. D. McCurdy, M. T. Yeung, K. L. Marsh, S. I. Khan, R. B. Kaner, Y. Rubin, *Chem* **2016**, *1*, 78–90.
- [22] F. Li, E. Shishkin, M. A. Mastro, J. K. Hite, C. R. Eddy Jr., J. H. Edgar, T. Ito, *Langmuir* **2010**, *26*, 10725–10730.
- [23] T. Kim, R. M. Crooks, M. Tsen, L. Sun, J. Am. Chem. Soc. 1995, 117, 3963–3967.
- [24] B. P. Krishnan, S. Mukherjee, P. M. Aneesh, M. A. G. Namboothiry, K. M. Sureshan, *Angewandte Chemie International Edition* **2015**, *55*, 2345–2349.
- [25] J. Hlavatý, L. Kavan, N. Kasahara, A. Oya, Chem. Commun. 2000, 0, 737–738.
- [26] L. Ding, S. V. Olesik, *Nano Lett.* **2004**, *4*, 2271–2276.
- [27] T. Luu, Y. Morisaki, N. Cunningham, R. R. Tykwinski, J. Org. Chem. 2007, 72, 9622–9629.
- [28] Q. Zheng, J. C. Bohling, T. B. Peters, A. C. Frisch, F. Hampel, J. A. Gladysz, *Chemistry A European Journal* **2006**, *12*, 6486–6505.
- [29] Q. Zheng, J. A. Gladysz, J. Am. Chem. Soc. **2005**, 127, 10508–10509.
- [30] S. M. E. Simpkins, M. D. Weller, L. R. Cox, *Chem. Commun.* **2007**, *106*, 4035–4037.
- [31] C. Klinger, O. Vostrowsky, A. Hirsch, Eur. J. Org. Chem. 2006, 2006, 1508–1524.
- [32] S. Eisler, A. D. Slepkov, E. Elliott, T. Luu, R. McDonald, F. A. Hegmann, R. R. Tykwinski, *J. Am. Chem. Soc.* **2005**, *127*, 2666–2676.
- [33] R. Dembinski, T. Bartik, B. Bartik, M. Jaeger, J. A. Gladysz, J. Am. Chem. Soc. 2000, 122, 810–822.
- [34] P. Siemsen, R. C. Livingston, F. Diederich, *Angewandte Chemie International Edition* **2000**, *39*, 2632–2657.
- [35] S. Schrettl, E. Contal, T. N. Hoheisel, M. Fritzsche, S. Balog, R. Szilluweit, H. Frauenrath, *Chem. Sci.* **2015**, *6*, 564–574.
- [36] W. A. Chalifoux, R. R. Tykwinski, *Compte Rendus Chimie* **2009**, *12*, 341–358.
- [37] L. Su, J. Dong, L. Liu, M. Sun, R. Qiu, Y. Zhou, S.-F. Yin, J. Am. Chem. Soc. 2016, jacs.6b07984-4.
- [38] Y. Morisaki, T. Luu, R. R. Tykwinski, *Organic Letters* **2006**, *8*, 689–692.
- [39] S. Schrettl, C. Stefaniu, C. Schwieger, G. Pasche, E. Oveisi, Y. Fontana, A. F. I. Morral, J. Reguera, R. Petraglia, C. Corminboeuf, et al., *Nature Chemistry* **2014**, *6*, 468–476.
- [40] T. N. Hoheisel, H. Frauenrath, *Organic Letters* **2008**, *10*, 4525–4528.
- [41] A. Michaelis, R. Kaehne, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1048–1055.
- [42] J. K. Augustine, A. Bombrun, A. B. Mandal, P. Alagarsamy, R. N. Atta, P. Selvam, *Synthesis* **2011**, *2011*, 1477–1483.
- [43] A. Gianella, A. J. Mieszawska, F. J. M. Hoeben, H. M. Janssen, P. A. Jarzyna, D. P. Cormode, K. D. Costa, S. Rao, O. C. Farokhzad, R. Langer, et al., *Chem. Commun.* 2013, 49, 9392–9394.
- [44] L. W. Bieber, M. F. da Silva, P. H. Menezes, *Tetrahedron Letters* **2004**, *45*, 2735–2737.
- [45] S. Szafert, J. A. Gladysz, *Chem. Rev.* **2003**, *103*, 4175–4206.
- [46] L. D. Movsisyan, M. D. Peeks, G. M. Greetham, M. Towrie, A. L. Thompson, A. W. Parker, H. L. Anderson, *J. Am. Chem. Soc.* **2014**, *136*, 17996–18008.
- [47] C. D. Bain, E. B. Troughton, Y. T. Tao, J. Evall, G. M. Whitesides, R. G. Nuzzo, *J. Am. Chem. Soc.* **1989**, *111*, 321–335.
- [48] A. Pathak, A. Bora, K.-C. Liao, H. Schmolke, A. Jung, C.-P. Klages, J. Schwartz, M. Tornow, *Journal of Physics: Condensed Matter* **2016**, *28*, 094008.
- [49] M. James, T. A. Darwish, S. Ciampi, S. O. Sylvester, Z. Zhang, A. Ng, J. J. Gooding, T. L. Hanley, *Soft Matter* **2011**, *7*, 5309–5318.