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Feature Article

Modular chemical tools for advanced macromolecular engineering

Jean-François Lutz [a,*], Helmut Schlaad [b,**]

[a] Research Group Nanotechnology for Life Science, Fraunhofer Institute for Applied Polymer Research, Geiselbergstrasse 69, 14476 Potsdam, Germany
[b] Max Planck Institute of Colloids and Interfaces, Colloid Department, Research Campus Golm, 14424 Potsdam, Germany

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Abstract

Contemporary polymer science requires, more than ever, simple and efficient chemical reactions for constructing complex macromolecular or supramolecular structures. The present feature article highlights our recent efforts to develop modular synthetic platforms in macromolecular synthesis. As examples, the macromolecular engineering possibilities of two ''click'' reactions (i) the copper-catalyzed cycloaddition of azides and terminal alkynes and (ii) the radical addition of mercaptans onto vinyl double bonds are discussed in detail herein.

Keywords: Living/controlled polymerizations; ''Click'' chemistry; Bio-hybrids

1. Introduction

Macromolecular chemistry requires, perhaps more than any other synthetic disciplines, simple, efficient and versatile chemical reactions [1]. Indeed, despite the enormous progress that has been made in this field of research over the last few decades, synthetic macromolecules remains generally rather undefined in comparison to biopolymers such as proteins or nucleic acids. Such limitations of polymer chemistry may surprise many non-specialists since modern organic synthesis offers practical solutions for the preparation of chemo-, regio- and stereo-controlled low molecular weight compounds. However, these chemical tools are not always readily transferable from the molecular scale to the macromolecular scale [1]. For instance, in standard organic synthesis, low-yield or unspecific chemical steps lead to the formation of distinct byproducts, which can be to some degree isolated and purified. Similar reactions at the macromolecular level lead to ill-defined polymer structures.

Hence, the set of chemical reactions commonly used for synthesizing or modifying polymers is, by necessity, limited to established straightforward tools. Yet, what appears at first as a significant limitation may in fact be an important advantage. For instance, Nature is only using a few chemical reactions and a very small library of monomers (20 amino acids and a few sugars and nucleobases) for synthesizing biopolymers and biological materials of remarkable structural and functional perfection. Through billions of years of optimization, nature only selected robust chemical tools, which are perfectly adapted to earth's environmental conditions. Such selective approach may also be relevant in synthetic chemistry and could be an efficient strategy for building the materials of the future. Some recent trends in chemical sciences, such as the ''click'' chemistry concept introduced by Sharpless and coworkers, emphasize this aspect [2]. The term ''click'' refers to versatile, efficient, specific and energetically favored chemical reactions, which could become universal tools in synthetic chemistry. This appealing concept was first proposed for low molecular weight organic synthesis and, in particular, for the important fields of combinatorial science and drug discovery [3]. However, ''click'' chemistry became also lately extremely popular in polymer and materials' sciences [4–8]. The rapid adoption of this concept in macromolecular chemistry is after

* Corresponding author.
** Corresponding author. Tel.: +49 331 567 9514; fax: +49 331 567 9502.
E-mail addresses: lutz@iap.fhg.de (J.-F. Lutz), schlaad@mpikg.mpg.de (H. Schlaad).

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all not very surprising since, as discussed above, polymer science requires universal synthetic tools.

The objective of the present feature article is to describe efficient chemical reactions, which have been recently shown to be modular tools for polymer synthesis. In particular two versatile reactions, namely the copper-catalyzed 1,3-dipolar cycloaddition of azides and alkynes (a well-established example of ''click'' chemistry) and the free-radical addition of ω-functional mercaptans on double bonds, which have been intensively studied in our groups, will be discussed in details [4,9]. Both reactions allow wide possibilities of macromolecular engineering such as, for example, the synthesis of defined telechelics, functionalized block copolymers and bio-hybrids structures (i.e. polymer bioconjugates) [10–12]. The potential impact of these modular reactions in modern polymer chemistry, but also in nanosciences (e.g. colloids, surface modifications, stimuli-responsive materials), will be discussed and illustrated by various examples taken from the recent literature.

2. Modular chemical reactions: how to select a few from many?

The definition of a modular chemical reaction is inevitably very subjective, as many organic transformations may play important and versatile roles in polymer science. Thus, it is important at this stage to list some essential criteria, which, in our opinion, make a reaction particularly relevant for macromolecular chemistry. In fact, the four words listed below describe clearly the current expectations of polymer chemists.

(i) Efficiency: as explained in Section 1, high reaction yields are mandatory in macromolecular chemistry. Indeed, incomplete steps or reactions requiring a large excess of one reactant lead to extra purification procedures. This aspect is generally not a big issue when a macromolecule is reacted with low molecular weight compounds, as several straightforward methods (e.g. precipitation, dialysis, centrifugation) allow isolation of macromolecules from low molecular weight mixtures. On the other hand, purification aspects are usually much more problematic in the case of reactions involving several macromolecular reactants (e.g. macromolecular coupling). The purification of macromolecular mixtures (e.g. using fractionation or chromatography) is usually not trivial. Thus, in those cases, high yield reactions using only stoichiometric quantities of reactants are highly valuable.

(ii) Selectivity: chemo-, regio- and stereo-selectivity are very important features in polymer chemistry. Indeed, the nanoscale morphologies and the macroscopic properties of macromolecules strongly depend on the regularity of their molecular structure [13]. For instance, some complex self-assembly processes are only achievable with extremely well-defined macromolecules [10,14]. In this context, the use of nonspecific organic reactions should be avoided. A good example for illustrating the importance of selectivity in macromolecular synthesis is the side-chain functionalization of reactive polymer backbones. In this particular case, highly specific reactions are beneficial since competitive reactions may result in the random formation of very different types of side-chains (see following paragraphs for some practical examples).

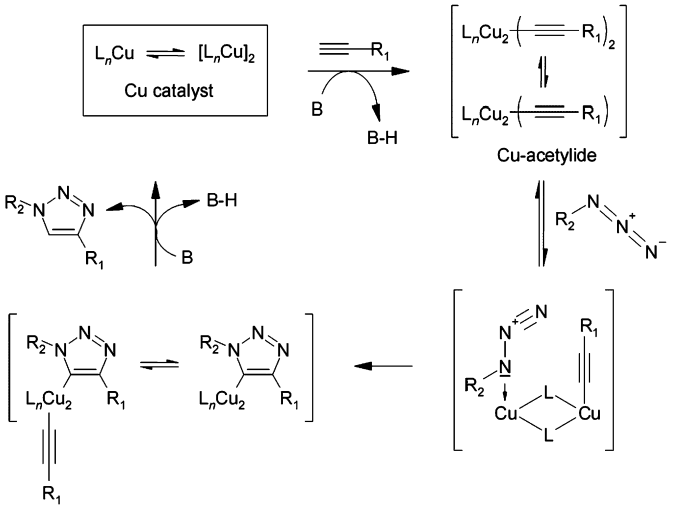
(iii) Versatility: this particular point is very important nowadays, as the range of applications of polymer materials grew extensively within the last few decades. Modern specialty polymers may be synthesized or modified in a wide variety of experimental conditions (e.g. in polar or apolar media, in biological conditions, in confined environments). For instance, due to the recent explosion of environmental, biomedical, and biotechnology research, macromolecular chemistry in polar environments is more important than ever. Thus, the development of versatile synthetic platforms, applicable to various materials and in various environments, is timely and imperative. In particular, the search for highly chemoselective tools, allowing direct modification of unprotected functional-materials, is essential.

(iv) Simplicity: this last requirement may appear trivial, but in fact reflects a real change of minds in polymer chemistry. It is noteworthy that over the past few years, complicated reactions requiring either complex apparatus, harsh experimental conditions or high-purification techniques, have been less frequently studied than in the last century and slowly replaced by simpler tools (i.e. organic reactions, which can be performed at moderate temperatures (e.g. 25–40 °C), ambient pressure and under environmentally friendly conditions). Such straightforward reactions are, for example, valuable for the *in situ* modification of nanomaterials or biological systems.

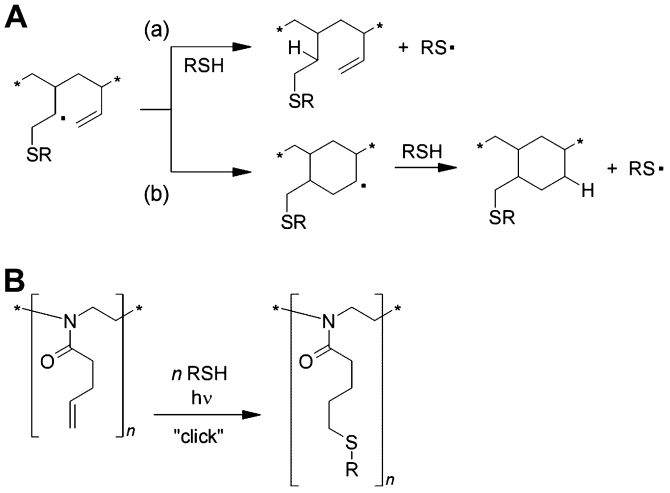
Several organic reactions meet the criteria listed above. For example, the formation of amide bonds using active ester chemistry is nowadays a very established tool in polymer chemistry, especially for applications at the interfaces between materials science and bio-sciences [12,15]. Other efficient coupling methods such as the Staudinger ligation or native chemical ligation are potentially versatile for macromolecular engineering [12,16]. However, more generally speaking, Sharpless classification of spring-loaded ''click'' reactions can be used as a guideline for selecting modular platforms [2]. The so-called ''click'' reactions may be ranked in four categories: (i) cycloadditions of unsaturated species (most commonly Huisgen, but also Diels–Alder transformations), (ii) nucleophilic ring-opening of strained heterocyclic electrophiles, (iii) carbonyl chemistry of the ''non-aldol'' type, and (iv) additions to carbon–carbon multiple bonds (e.g. addition of mercaptans onto vinyl double bonds) [2]. Among these types, several reactions (e.g. Diels–Alder chemistry) have been widely explored in polymer chemistry many years before their ''click'' upgrade [17–19]. On the other hand, some reactions have been clearly reestablished and boosted by the ''click'' concept. The most obvious example is the

copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), a reaction generally regarded as the archetype of "click" chemistry (Scheme 1). In the absence of transition metal catalyst, 1,3-dipolar Huisgen cycloadditions of azides and terminal alkynes are, in most cases, not regioselective and usually rather slow [20]. However, Meldal and coworkers reported that the use of catalytic amounts of copper(I), which can bind to terminal alkynes, leads to fast, highly efficient and regioselective azide-alkyne cycloadditions at room temperature in organic medium [21]. Moreover, shortly after, Sharpless et al. demonstrated that CuAAC can be successfully performed in polar media such as *tert*-butyl alcohol, ethanol or pure water [22]. These two important reports led to a remarkable renaissance of Huisgen cycloadditions in synthetic chemistry. Hence, CuAAC has been exponentially investigated within the last few years in organic synthesis, inorganic chemistry, polymer chemistry and biochemistry [4,6,7,23–26]. Such rapid adoption of CuAAC in almost all areas of chemistry is rather unique and illustrates the versatility of this "click" reaction. Several examples of macromolecular engineering and material design employing CuAAC are described in next paragraphs.

The radical addition of mercaptans (RSH) onto vinyl double bonds could be well considered as a click reaction (type (IV)) as it can proceed smoothly in quantitative yields and be regioselective (i.e. anti-Markovnikov) [27,28]. However, the addition onto for instance 1,2-polybutadiene suffers from a seemingly unavoidable side reaction of the intermediate radical species (Scheme 2A). The desired route is that the radical formed by the addition of RS• onto the double bond abstracts a hydrogen atom from another RSH molecule (pathway a). But prior to hydrogen transfer, the radical may add to another double bond in its vicinity, leading to the formation of a cyclic unit (pathway b). The degree of modification is therefore less than quantitative (<85%) at a full conversion of double bonds [29]. The undesired pathway b could be eliminated by increasing the distance between intermediate radical and neighboring double bond, thus replacing 1,2-polybutadiene by for instance poly[2-(3-butenyl)-2-oxazoline]; this polymer



Scheme 1. Stepwise mechanism proposed for the copper-catalyzed 1,3-dipolar "click" cycloaddition of azides and alkynes (L = ligand, B = base) [81].



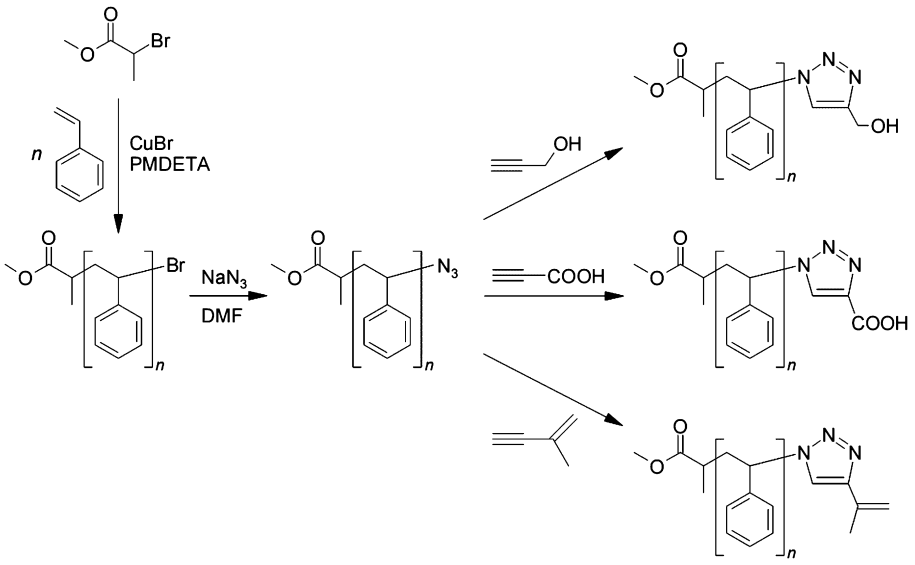
Scheme 2. Proposed mechanisms for the free-radical addition of ω-functional mercaptans onto (A) 1,2-polybutadiene and (B) poly[2-(3-butenyl)-2-oxazoline] [29,30,55].

is available with low polydispersity ($M_w/M_n \sim 1.1$) through controlled cationic isomerization polymerization of 2-(3-butenyl)-2-oxazoline. The radical addition of a mercaptan onto poly[2-(3-butenyl)-2-oxazoline] has the characteristics of a click reaction (Scheme 2B). The "thio-click" reaction can be performed under economic ([RSH]/[C=C] ~ 1.2–1.5, no transition metal additives) and mild conditions (*in situ* generation of radicals with UV light at room temperature) and goes to completion within one day. Well-defined hydrophobic fluoropolymers can be prepared in the same way as water-soluble polymers or glycopolymers, starting from readily available materials [30].

3. Examples of macromolecular engineering using modular reactions

Modular chemical reactions can be used for three different purposes in macromolecular chemistry: (i) as a polymerization step in a chain- or step-growth polymerization, (ii) as a reaction for the chain-end, side-chain or site-specific modification of preformed macromolecules and (iii) as a ligation tool for the covalent coupling of macromolecular segments [11]. In the present paragraph, we will mainly concentrate on the last two aspects.

Copper-catalyzed Huisgen cycloadditions have been recently extensively studied by polymer chemists for the synthesis of functional polymers (either end-functional or side-functional). The post-functionalization of synthetic polymers is an important feature of macromolecular engineering as many polymerization mechanisms are rather sensitive to the presence of bulky or functional groups. For example, a wide variety of telechelic polymers (i.e. polymers with defined chain-ends) can be efficiently prepared using a combination of atom transfer radical polymerization (ATRP) and CuAAC. This strategy was independently reported in early 2005 by van Hest and Opsteen [31], Lutz et al. [32], and Matyjaszewski et al. [33]. Such step was important since ATRP is a very popular



Scheme 3. General strategy proposed for the "click" functionalization of the ω-chain ends of well-defined polystyrene prepared using atom transfer radical polymerization (ATRP) [32].

polymerization method in modern materials science [34,35]. Indeed, ATRP is a facile technique, which allows the preparation of well-defined polymers with narrow molecular weight distribution, predictable chain length, controlled microstructure, defined chain-ends and controlled architecture [36–41]. However, the range of possibilities of ATRP can be further broadened by CuAAC. For instance, the ω-bromine chain-ends of polymers prepared by ATRP can be transformed into azides by nucleophilic substitution and subsequently reacted with functional alkynes (Scheme 3) [32]. Due to the very high chemoselectivity of CuAAC, this method is highly modular and may be used to synthesize a wide range of ω-functional polymers. Moreover, the formed triazole rings are not "passive" spacers but interesting functions exhibiting H-bonds capability, aromaticity and rigidity.

The strategy depicted in Scheme 3 can be applied to polystyrene derivatives [31–33], poly(acrylates) [42–44] and eventually poly(methacrylates), although the latter are usually more difficult to transform into azido-functionalized polymers [36]. ^{1}H NMR and IR studies of the "click" functionalization of polystyrene and poly(acrylates) models indicated that both transformation steps (i.e. azide substitution and CuAAC) are, in almost all cases, quantitative [32,42,44,45]. However, in such ω-modification approach, the fraction of functionalized polymer chains can never reach 100%, as atom transfer radical polymerizations are, by essence, subject to termination reactions (i.e. only the bromine end-capped dormant chains can be functionalized in this process) [32]. But a degree of functionalization as high as 95% can be obtained when ATRP is performed under conditions that minimize terminations and side reactions [46,47]. Alternatively, azide- or alkyne-functional ATRP initiators can also be used (i.e. α-modification approach) [31,33,48]. Nevertheless, the ω-strategy is the only one applicable when polymer brushes are grown by ATRP from a planar or colloidal surface [40]. Furthermore, ATRP/CuAAC chain-end strategies may be further exploited for the synthesis of defined macromolecular architectures such as block copolymers [31,49], graft copolymers [44], macromolecular brushes [50], stars [51], miktoarm stars [52], macrocycles [53] or networks [42].

The side-chain "click" functionalization of reactive backbones having alkyne- or azide-repeat units was also reported [4,6,8]. Generally speaking, this approach seems to be very efficient, even for attaching very bulky substituents such as dendrons [54]. However, an interesting metal-free alternative for synthesizing polymers with defined side-chains is the radical addition of mercaptans onto polymeric backbones with pendant double bonds such as 1,2-polybutadiene or poly[2-(3-butenyl)-2-oxazoline] [9,29,30,55]. Schlaad and coworkers demonstrated that this approach is versatile and can be applied to large libraries of functional thiols. For instance, mercaptan additions proceed smoothly in the presence of various unprotected chemical functions such as esters, primary amines, carboxylic acids, alcohols, sugars and perfluoroalkyl groups [30,55]. However, as aforementioned, the modifications are usually not quantitative in the case of 1,2-polybutadiene, as cyclic units may be formed (Scheme 2). Hence, modified polybutadienes have usually the same narrow molecular weight distribution as their parent polymer backbones but exhibit chemical defects. In comparison, the radical addition of mercaptans onto poly[2-(3-butenyl)-2-oxazoline] seems to proceed without undesirable side reactions [30]. ^{1}H NMR and IR studies indicated that the thio-modifications of this polymer are generally quantitative and highly regioselective (no Markovnikov addition products detected in NMR). Moreover this strategy is not restricted to homopolymers but can be also used for modifying well-defined block or gradient copolymers.

4. Construction of bio-hybrid materials

Bio-hybrid polymers (also referred to as polymer bioconjugates or macromolecular chimeras), which combine the

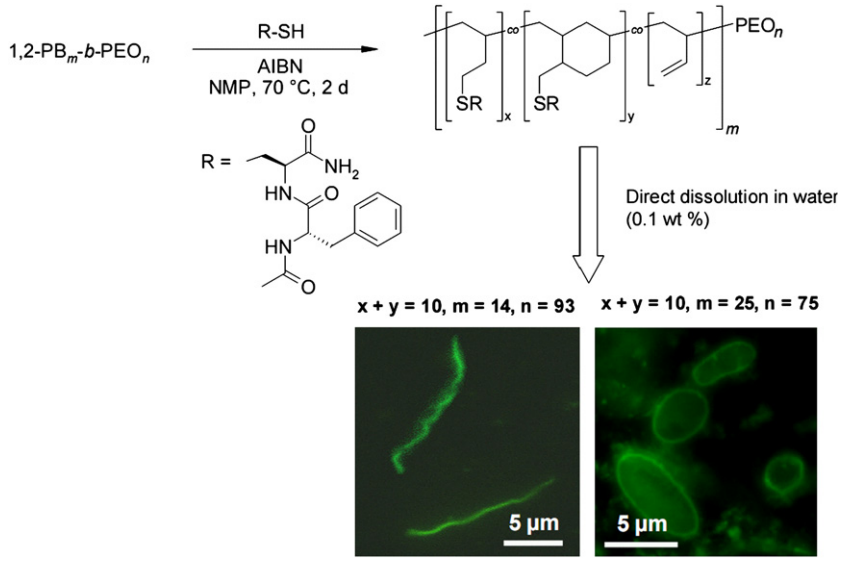


Fig. 1. Synthesis of bio-hybrid amphiphiles by radical addition of cysteine-based dipeptides onto 1,2-polybutadiene-*block*-poly(ethylene oxide)s and fluorescence microscopy images of self-assembled aggregates in aqueous solution [60].

properties of synthetic and biological materials in a single macromolecule, have gained considerable importance in modern materials science and biotechnology [12,14]. However, their synthesis remains challenging since it requires versatile chemical tools at the interface of biochemistry, organic synthesis and polymer science. In that regard, CuAAC is indeed an appealing platform for synthesizing bio-hybrids. In particular, two important features make this reaction particularly attractive for bioconjugation purposes. Firstly, as mentioned in paragraph 2, CuAAC proceeds well in aqueous medium and therefore may be efficiently performed under physiological conditions. Perhaps even more importantly, CuAAC is an extremely chemoselective reaction and can therefore be used for modifying highly functional biomolecules such as polypeptides, nucleic acids or polysaccharides [4,56–58]. Furthermore, highly complex biological entities such as transport proteins, enzymes, viruses, bacteria or cells may also be conjugated to polymers or low molecular weight functional groups using azide/alkyne click chemistry. However, such chemical modifications of biological assemblies should be cautiously characterized since many reactants (e.g. transition metal catalyst) may induce denaturation, disassembly or loss of biological activity. Detailed informations about ''click'' bioconjugation may be found in several recent reviews [4,6].

Lutz and coworkers studied the ''click'' cycloaddition of short peptides such as RGD (cell adhesion sequence), TAT (protein transduction domain) or INF7 (membrane disruption peptide) with well-defined synthetic polymers synthesized by ATRP [43,59]. Typically, ω-azido-functionalized polymers (*vide supra*) were reacted with alkyne-functionalized peptides. Such CuAAC ligations can be performed in organic medium with protected peptides (i.e. the protecting side-groups of the amino acids are not cleaved after solid-phase synthesis) or directly in aqueous medium with fully deprotected structures. In both cases, a high yield of bioconjugation can be obtained. However, the use of protected peptides greatly facilitates the characterization of the formed polymer bioconjugates (e.g. using SEC in organic medium) [43,59].

L-Cysteine-containing oligopeptides can be readily added onto 1,2-polybutadiene-based block copolymers. However, the radical addition step does not occur in the absence of side reactions (Scheme 2B) and with less than quantitative conversion of double bonds. Nevertheless, this approach enables one to generate a platform of chiral bio-hybrid amphiphiles with narrow molecular weight distributions and tailored functionalities. Also, one can readily produce micron-sized helical superstructures or giant vesicles by direct dissolution of the amphiphile in water (Fig. 1) [60].

Another very important class of bio-hybrid polymers is glycopolymers [61]. Well-defined glycopolymers with a synthetic poly(methacrylate) backbone and pendant sugar moieties can be prepared employing a combination of ATRP and CuAAC, as demonstrated by Haddleton and coworkers [62]. A simpler way towards glycopolymers is the radical addition of commercial 1-thio-sugar derivatives onto polybutadiene-based polymers. The degree of functionalization may be in the range of 55–65% at full conversion of double bonds, which is enough to make hydrophobic polymers dispersable in water under formation of vesicles or ''glycosomes'' [63,64]. The photoaddition of 2,3,4,6-tetra-*O*-acetyl-1-thio-glucopyranose onto poly[2-(3-butenyl)-2-oxazoline], on the other hand, proceeds in the complete absence of side reactions, as indicated by spectroscopy and SEC (Fig. 2) [30].

5. Modification of block copolymers assemblies

Macromolecular amphiphiles and their aggregates in water are an increasingly important aspect of modern colloidal science [13]. Indeed, macromolecular surfactants such as amphiphilic block copolymers or polysoaps spontaneously self-assemble in selective solvents into a variety of interesting and useful nanoscale morphologies [65–73]. Overall, the

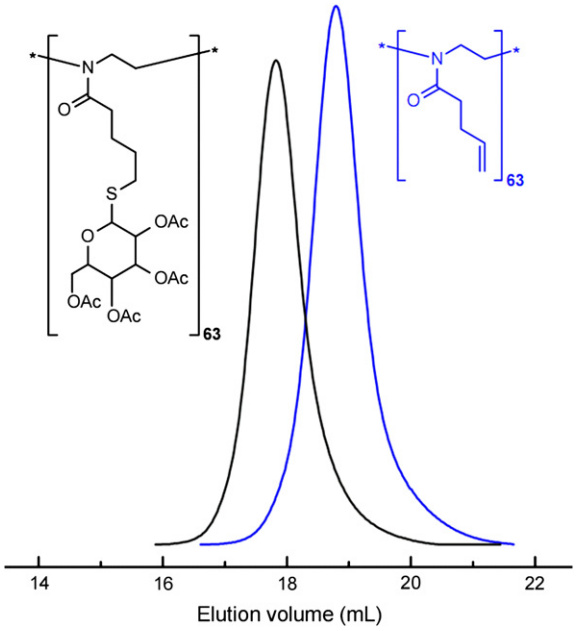


Fig. 2. Chemical structures and SEC chromatograms (eluent: THF) of a poly[2-(3-butenyl)-2-oxazoline] with a number-average of 63 repeat units (right) and the derived glycopolymer obtained by ''thio-click'' addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-glucopyranose [30].

micellization of macromolecular amphiphiles is a typical example of ''bottom-up'' approach. Polymeric surfactants are generally designed, synthesized and characterized at the molecular level and subsequently assembled into colloidal structures. Still, in some particular cases, the *in situ* modification of preformed micelles may be of interest. For example, post-functionalization is sometimes required in biomedical applications such as targeted drug- or gene-delivery when functional targeting moieties interact with encapsulated substances. However, the chemical modification of preformed micellar aggregates is indeed limited by the nature of the dispersion medium and therefore requires modular chemical reactions, which can be performed in dilute aqueous solutions and at relatively moderate temperatures (i.e. room or physiological temperature).

The copper-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes is potentially a very interesting reaction for modifying *in situ* polymeric micelles. Wooley and coworkers first pointed out the advantages of ''click'' CuAAC for functionalizing or crosslinking block copolymer micelles, composed of a polystyrene core and a poly(acrylic acid) shell [74–76]. Additionally, the Lutz group recently studied the *in situ* shell-functionalization of biocompatible micelles composed of a cholesterol-based hydrophobic core and a thermoresponsive PEG-based polymer shell (Fig. 3) [45,77–79]. The biocompatible surfactants cholesterol-*b*-poly(oligo(ethylene glycol) methyl ether acrylate) were prepared using ATRP and their bromine chain-ends were transformed into an azide moiety. CuAAC was performed directly on the micelles corona at room temperature and in dilute aqueous solutions and led after 24 h of reaction to a percent yield of corona functionalization higher than 95. Very recently, van Hest and coworkers demonstrated that the alkyne-azide approach could also be exploited for functionalizing *in situ* polymersomes (i.e. block-copolymer vesicles) [80].

6. Outlook

The trends and results discussed above indicate that modular synthetic reactions such as CuAAC or the addition of mercaptans on double bonds have a great potential for advanced macromolecular design (e.g. synthesis or modification of defined macromolecular architectures, polymer bioconjugates

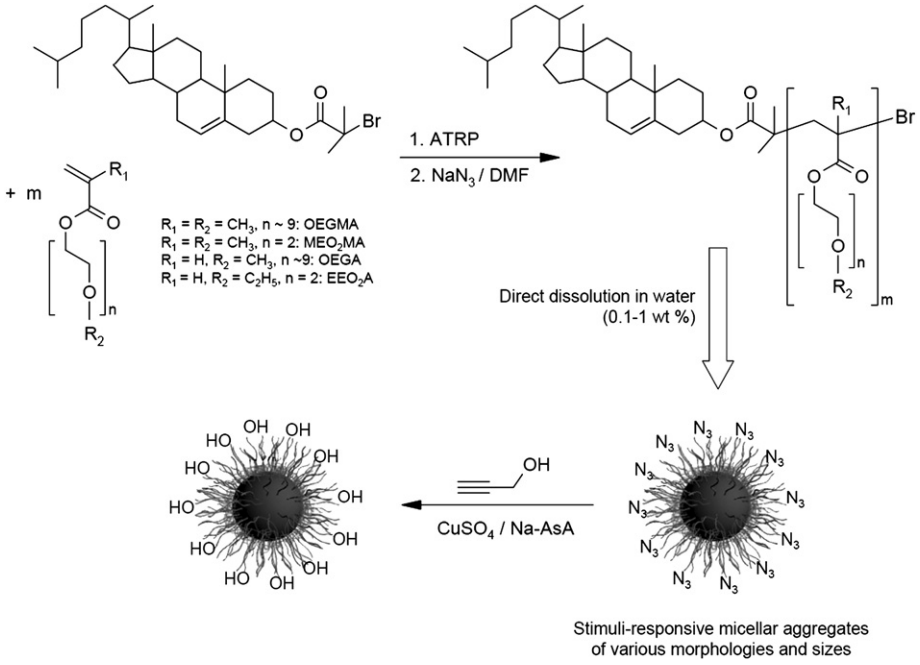


Fig. 3. Synthesis of azido-functional biocompatible macrosurfactants and their *in situ* ''click'' functionalization in dilute aqueous medium [45].

or self-assembled block copolymers). Although sometimes overestimated, the recent success of these reactions corresponds to a real need for versatility in modern polymer science. Indeed, such novel modular platforms allow to cross the traditional boundaries between synthetic disciplines (e.g. macromolecular chemistry, biochemistry, low molecular weight organic synthesis, inorganic chemistry) and therefore open a broad avenue for the design of novel generations of highly organized and highly functional nanomaterials.

Acknowledgments

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Jean-François Lutz was born in Paris, France in 1972. After obtaining his BSc. and MSc. degrees from the University Pierre et Marie Curie (Paris VI), he moved to Montpellier (France), where he completed his Ph.D. degree under the supervision of Prof. Bernard Boutevin. Afterwards, he joined the research group of Prof. Krzysztof Matyjaszewski at Carnegie-Mellon University (Pittsburgh, USA), where he worked for two years as a post-doctoral fellow. In late 2003, he joined the Fraunhofer Institute for Applied Polymer research (Potsdam-Golm, Germany) for leading the research group Nanotechnology for Life Science. His current research interests include the synthesis of polymer bioconjugates, the design of smart biocompatible polymers and the self-organization of macromolecules in aqueous medium.

Helmut Schlaad, born 1967 in Bad Kreuznach, Germany, studied chemistry at the University of Mainz, Germany, and received his diploma in 1993. He completed his Ph.D. in 1997 under the supervision of Prof. Axel H. E. Müller. After one year as a post-doctoral fellow in the group of Prof. Rudolf Faust at the University of Massachusetts, Lowell, USA, he joined the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany. He finished his habilitation and became a senior scientist in 2004. His research interests are directed towards the smart design of polymers and hierarchical structure formation of synthetic and bio-hybrid polymers.