Chapter 2
Theoretical Background and Literature Overview

As stated in the introduction, the present thesis is based on a combination of reversible-deactivation radical polymerization via the RAFT process and supramolecular CD host/guest complexes. The RAFT process provides the opportunity to generate polymers with specific endgroups, e.g. guest functionalities for CD. These polymers can subsequently be exploited for the formation of novel complex macromolecular architectures, e.g. block copolymers, star polymers or miktoarm star polymers. The underlying theoretical background is described in the following sections as well as an overview of CD mediated complex macromolecular architectures that have been published in the literature so far.

2.1 Reversible Addition-Fragmentation Chain Transfer Polymerization

2.1.1 Living Polymerization

A living polymerization is strictly speaking a chain propagation reaction that—after full monomer conversion—is still capable of propagation via addition of further monomer [2]. In an ideal case this occurs in polymerization reactions without any chain transfer and termination [3, 4]. Furthermore, the rate of initiation should be fast compared to the rate of propagation, which results in the synthesis of polymer chains with an overall similar degree of polymerization (D_p) [5]. Anionic and some cationic polymerizations are treated as classical/truly living polymerization, while the more recent atom transfer radical polymerization (ATRP) [6–8], nitroxide-mediated polymerization (NMP) [4, 9–11] and the RAFT polymerization [12–16] are treated as

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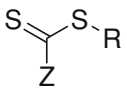


Fig. 2.1 General structure of a CTA/RAFT agent

polymerization with living characteristics, as controlled radical polymerization [17] or reversible-deactivation radical polymerization. All living polymerization techniques have in common that D_p increases linearly with monomer conversion, block copolymers can be formed via sequential monomer addition and low $Đ_m$ are achieved.

In the case of ATRP, radical chain ends are generated via a transition metal catalyzed one electron redox-process that leads to halide terminated dormant chains or radical bearing active chains [6]. An equilibrium between dormant and active species that is centered on dormant species controls the reaction. In NMP, the persistent radical effect is utilized [4]. A nitroxide acts as a radical trap for active chains. As the process of chain termination via a nitroxide is reversible, an activation/deactivation equilibrium is formed. In both processes, ATRP and NMP, a small amount of active species leads to the minimization of radical termination events. The RAFT process is an alternative method to control radical polymerizations and achieves living behavior. Macromolecular design via the interchange of xanthates (MADIX) has an identical mechanism to RAFT yet uses slightly different controlling agents. Both methods were patented in 1998 [18, 19] and are utilized in polymer research very often since then [13, 14]. The RAFT process will be described in detail in the next sections.

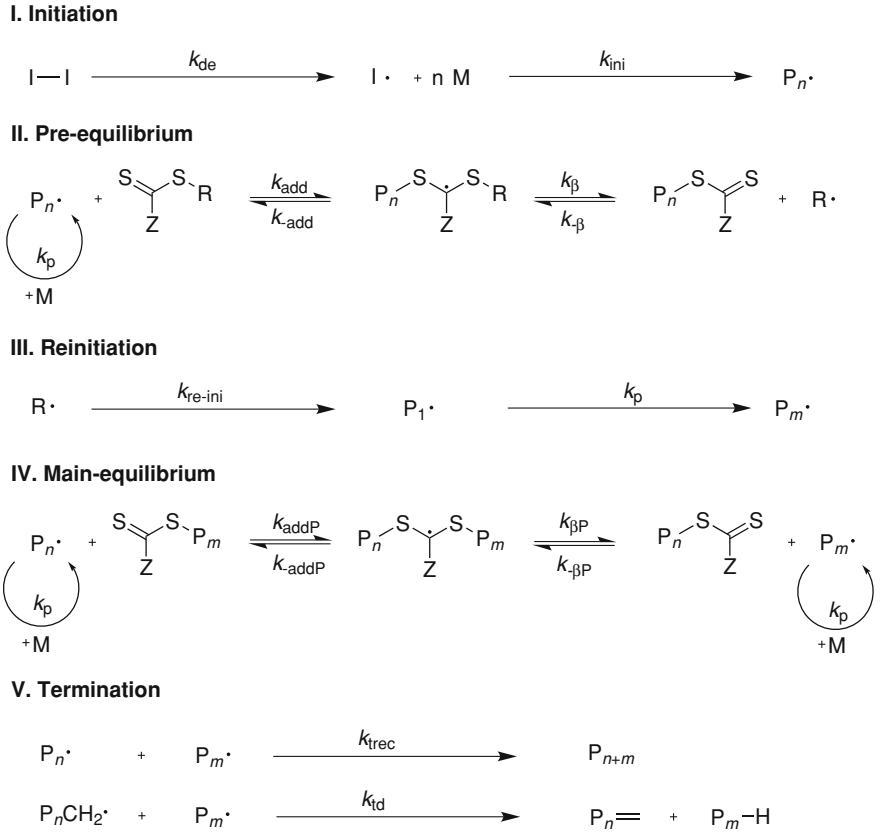
RAFT and MADIX differ substantially from the other controlled radical polymerizations, as for the control of the polymerization no persistent radical effect is utilized (refer to Sect. 2.1.2), leading to an increase in propagation rate compared to the other controlled radical polymerization techniques. The process is tolerant to functional monomers, e.g. acrylic acid or vinyl acetate (refer to Sect. 2.1.3), and is especially useful for the preparation of water-soluble polymers (refer to Sect. 2.1.4). The RAFT process, as the other living polymerization techniques, is a tool for the synthesis of complex macromolecular architectures, e.g. block copolymers or star polymers (refer to Sect. 2.1.5).

2.1.2 Mechanism and Kinetics

The central element in the RAFT process is the chain transfer agent (CTA) that allows for control on the polymerization.

The CTA is typically a thiocarbonyl thio compound featuring two substituents that are usually abbreviated as R- and Z-group (refer to Fig. 2.1). These two substituents have a profound influence on the reactivity of the CTA and the RAFT process can be varied via the modification of these substituents. The R-group is also called the radical leaving group and the Z-group is also called the stabilizing group [20, 21].

As depicted in Scheme 2.1 the RAFT equilibria do not create or terminate radicals. Except of the termination reactions, every reaction in the RAFT process

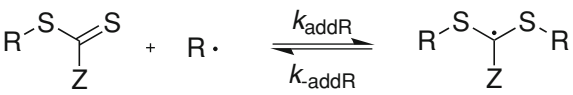


Scheme 2.1 Basic mechanism of the RAFT process

generates a radical. There are only bimolecular cooperative chain transfer reactions [22] and—in contrast to ATRP and NMP—no persistent radicals are involved that are endfunctionalizing polymers in a monomolecular process. Thus, no decrease in the polymerization rate should ideally occur from the RAFT process itself under the assumption that fragmentation and reinitiation are not rate defining. Nevertheless, often inhibition or slower propagation rates compared to conventional free radical polymerization are observed [13, 23]. The RAFT process can be divided into five distinct reaction sequences: Initiation, pre-equilibrium, reinitiation, main-equilibrium and termination. The mechanism of the RAFT process is depicted in Scheme 2.1.

The initiation occurs via the formation of primary radicals I· that form during the decay of a radical initiator I_2 with the rate coefficient k_{de}. The formed radicals react with monomers to short oligomeric chains P_n· with the rate coefficient k_{ini} until a radical reacts with a CTA molecule. The ratio of CTA to initiator should be high, especially when high endgroup functionalization is necessary, e.g. for chain extensions or complex macromolecular architecture formation. Furthermore, a high

Scheme 2.2 Reversible chain transfer in the RAFT process



initiator concentration has the drawback of an increased probability of termination reactions due to higher radical concentration [22].

The initiator derived chain adds to a CTA molecule with the rate constant k_{add}. Subsequently the thiocarbonyl centered radical undergoes β-fragmentation with the rate coefficient k_β, which leads to the formation of a free radical R· and a thiocarbonyl thio capped chain. The reaction of the formed radical R· with the rate coefficients k_{addR} and k_{-addR} with another CTA molecule (refer to Scheme 2.2) is usually neglible due to the short life time of the intermediate. In the case of slow fragmentation and side-reactions of the intermediate the reaction should be taken into account [13].

For the description of the chain transfer, the chain transfer constants C_{tr} and C_{-tr} are defined:

$$C_{tr} = \frac{k_{tr}}{k_p} = \frac{k_{add}}{k_p} \cdot \frac{k_\beta}{k_{-add} + k_\beta} \tag{2.1}$$

and

$$C_{-tr} = \frac{k_{-tr}}{k_i} = \frac{k_{-\beta}}{k_i} \cdot \frac{k_{-add}}{k_{-add} + k_\beta} \tag{2.2}$$

The transfer constants depend strongly on the R- and Z-group present in the CTA. The higher the value of C_{tr}, the better is the control of the polymerization [13, 21]. The formed R· radical should reinitiate the polymerization effectively. Furthermore, the R-group has to be a good homolytic leaving group and especially a better leaving group than the radical of the monomer so that fragmentation towards the R-group is preferred. Thus, a balance between reinitiation and leaving group ability has to be found for an effective RAFT process.

The main equilibrium starts when all CTA molecules have reacted. In the equilibrium, the intermediate fragments with the rate coefficient k_{-addP} to the macroradical P_n· or P_m· and a thiocarbonyl thio chain end. With the rate coefficient k_{addP}, the thiocarbonyl thio chain end adds a macroradical again. Whenever a fragmentation takes place, the macroradical can add new monomers with the propagation rate constant k_p. The kinetics of the main equilibrium can be described with the chain transfer constant C_{trP}, which can differ slightly from the chain transfer constant of the pre-equilibrium C_{tr}. If the polymer fragments P_n· or P_m· are treated as identical, the following assumption can be made:

$$k_{-addP} = k_\beta \tag{2.3}$$

which effects the chain transfer constant of the main equilibrium C_{trP} as follows:

$$C_{trP} = \frac{k_{addP}}{2 \cdot k_p} \tag{2.4}$$

For optimal control of the polymerization, C_{trP} should be high [13, 21], i.e. the higher C_{trP} the closer is the plot of D_P against conversion to linearity. Furthermore, $Đ_m$ is decreasing with higher C_{trP}. In the ideal case, there is the same probability for chain growth for all propagating chains, which leads to narrow molecular weight distributions. Following this mechanism a large quantity of the formed polymers should bear the thiocarbonyl thio Z-group on one end and the R-group on the other end. Furthermore initiator derived chains are formed in minor amounts.

Termination reactions occur intrinsically, as in free radical polymerization, radical recombination with k_{trec} and disproportionation with k_{td}.

As with all living polymerization techniques, D_p and the number average molecular mass M_n can be calculated from the conversion and the concentrations of initiator and monomer. D_p is based on the concentration of monomer [M], the concentration of CTA [CTA], the average number of chains that are formed in a termination reaction d, the initiator efficiency f and the initiator concentration [I_2]:

$$D_p = \frac{[M]_0 - [M]_t}{[CTA]_0 + d \cdot f([I_2]_0 - [I_2]_t)} \tag{2.5}$$

With a large excess of CTA compared to initiator follows:

$$D_p \approx \frac{[M]_0 - [M]_t}{[CTA]_0} \tag{2.6}$$

M_n can be calculated analogously with the molar mass of the monomer m_M and the molar mass of the CTA m_{CTA}:

$$M_n = \left(\frac{[M]_0 - [M]_t}{[CTA]_0 + d \cdot f([I_2]_0 - [I_2]_t)} \cdot m_M\right) + m_{CTA} \tag{2.7}$$

A simplification analogous to the calculation of D_p leads to:

$$M_n \approx \left(\frac{[M]_0 - [M]_t}{[CTA]_0} \cdot m_M\right) + m_{CTA} \tag{2.8}$$

In this case a linear relation between M_n or D_p and the monomer conversion is evident, which is characteristic for polymerizations with living character. In an ideal RAFT process the formed thiocarbonyl thio functionalized macromolecule can be reinitiated for chain extension. Too high initiator concentrations lead to the formation of unreactive chains, as the degree of initiator functionalized polymers is increasing. As mentioned earlier, CTAs are often sulfur containing thiocarbonyl thio compounds that have to be chosen according to the monomer. For an efficient RAFT polymerization, the choice of the respective R- and Z-group are crucial. The RAFT agent needs a reactive C–S double bond, which results in high k_{add} values. The intermediate radicals should ideally fragment rapidly, based on a weak S–R bond which leads

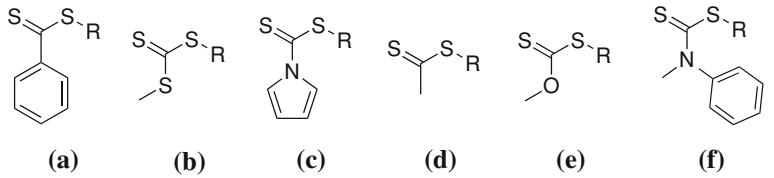


Fig. 2.2 Different types of CTAs [13]

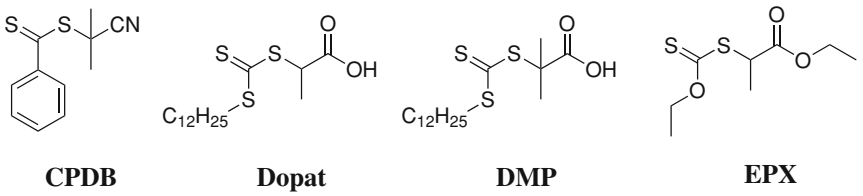


Fig. 2.3 Commonly utilized CTAs (**CPDB** 2-cyano-2-propyl benzodithioate; **Dopat** 2-((dodecylsulfanyl)carbonothioyl)sulfanyl propionic acid; **DMP** 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid; **EPX** ethyl 2-((ethoxycarbonothioyl)thio)propanoate)

to a large k_β value. Furthermore, the intermediate should partition in favor of the products, i.e. $k_\beta > k_{-\text{add}}$ and R· should effectively reinitiate the polymerization:

In Fig. 2.2 different Z-groups for CTAs are presented, e.g. aromatic (a) or aliphatic (d) dithioesters, trithiocarbonates (b), xanthates (e) and dithiocarbamates (c and f). The rate coefficients for addition and the transfer constants decrease from left ot right [20, 22, 24]. Via the Z-group, the addition and fragmentation rates are modified. The R-group has to be a good radical leaving group that is able to reinitiate the polymerization. Common R-groups include tertiary carbon atoms, e.g. in a cyanoisopropyl group, a cumyl group or an *iso*-butyric acid, or secondary carbon atoms, e.g. in a benzylic group or a *iso*-propionic acid.

2.1.3 Applicability of the Method and Reaction Conditions

The RAFT process gives the opportunity to perform reversible-deactivation radical polymerizations with a large variety of monomers, e.g. styrenic monomers, (meth)acrylates, (meth)acrylamides, vinyl acetate and *N*-vinyl monomers. A tertiary cyanoalkyl dithiobenzoate can act as CTA for styrene (Sty) and methyl methacrylate (MMA) (refer to compound **CPDB** in Fig. 2.3).

Another common class of CTAs are trithiocarbonates connected to tertiary or secondary carboxylic acids or esters (refer to the compounds **Dopat** or **DMP** in Fig. 2.3) that can be used to polymerize styrenics, acrylates or acrylamides. Xanthates (refer to compound **EPX** in Fig. 2.3) or cyanoalkyldithiocarbamates can be utilized

in the polymerization of vinyl acetate or *N*-vinyl monomers, e.g. *N*-vinylpyrrolidone or *N*-vinylcarbazole.

The reaction conditions can usually be adopted from the corresponding conventional free radical polymerization with a commonly used polymerization temperature ranging from ambient temperature to 140 °C. Usually, organic solvents are utilized, yet protic solvents such as alcohols or water can be utilized as well. Furthermore, bulk or emulsion polymerizations are described in the literature [13]. For the initiation every radical source is in principle utilizable [18], but in most cases thermal initiators are employed, e.g. 2,2′-azo-bis-(isobutyronitril) (**AIBN**). Other initiation methods are self-initiation [25, 26], UV-irradiation [27], γ irradiation [28] or a plasma field [29].

2.1.4 Preparation of Water-Soluble Polymers via RAFT Polymerization

RAFT polymerization is arguably the most useful controlled radical polymerization technique for the synthesis of water-soluble polymers [30]. In principle a polymerization in organic solvents or directly in water is possible. For the polymerization in water several water-soluble CTAs and initiators are available (refer to Fig. 2.4). In the case of organic solvents as reaction media a usual RAFT polymerization can be conducted as long as the monomer and polymer are soluble in the respective organic solvent. This is true for some of the mostly used monomers, e.g. *N*-isopropylacrylamide (**NIPAAm**), **DEAAm**, *N*,*N*-dimethylacrylamide (**DMAAm**) or *N*,*N*-dimethylaminoethyl methacrylate (**DMAEMA**). Nevertheless, problems arise when ionic or very hydrophilic monomers are considered that are only soluble in water or at least their corresponding polymers, e.g. styrene sulfonate [31], 2-acrylamido-2-methylpropansulfonic acid (**AMPS**) [32], (3-methacryloylamino-propyl)-(2-carboxy-ethyl)-dimethyl-ammonium (carboxybetaine methacrylamide) (**CBMAA-3**) [33] or acrylamide (**AAm**) [34]. Apart from the monomer choice, water as reaction solvent can have several advantages, when compared to organic solvents. Water is non-toxic, relatively cheap and has a high heat capacity. Some drawbacks are its high boiling point, thus water is not easy to recycle or to remove.

The CTA should be water-soluble in an aqueous polymerization, e.g. 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (**CTP**), 2-(((ethylthio)carbonothioyl)thio)-2-methylpropanoic acid (**EMP**) or 2-(1-carboxy-1-methylethylsulfanylthiocarbonyl sulfanyl)-2-methylpropionic acid (**CMP**). Nevertheless some side reactions are known that lead to less well defined polymers. McCormick and coworkers spent significant effort to study RAFT polymerization in water. At high temperatures and under neutral or basic conditions the CTA can undergo hydrolysis [30, 35, 36]. In the case of the polymerization of acrylamides, aminolysis can happen after hydrolysis of the respective monomer [30, 35]. Of course, hydrolysis of an amide is not a preferred process, yet when the equivalents of CTA to monomer are considered,

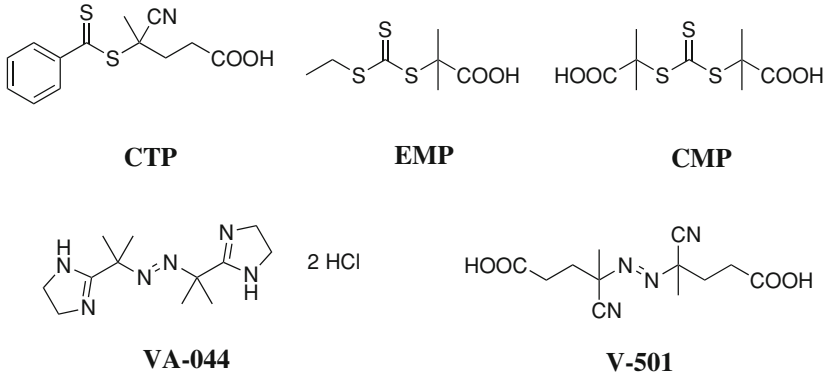


Fig. 2.4 Commonly utilized water-soluble CTAs and radical initiators (**CTP** 4-cyano -4-(phenylcarbonothioylthio)pentanoic acid; **EMP** 2-(((ethylthio)carbonothioyl)thio)-2-methylpropanoic acid; **CMP** 2-(1-carboxy-1-methylethylsulfanylthiocarbonylsulfanyl)-2-methylpropionic acid; **VA-044** 2,2′-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride; **V-501** 4,4'-azobis(4-cyanovaleric acid))

already a small portion of hydrolysis can lead to loss of CTA and thus control of the polymerization. Usually a higher molecular mass than expected and broader molecular mass distributions are observed. A possibility to overcome these issues is to polymerize in slightly acidic media, e.g. acetic acid buffer, at low temperatures or at best in acidic media and at low temperatures. In these cases even controlled RAFT polymerizations of acrylamides in water are possible [34, 37, 38].

Several monomer classes for water-soluble polymers are available (refer to Fig. 2.5) and can be chosen for the respective application [30, 39]. There are anionic monomers or monomers that can easily be deprotonated, e.g. styrene sulfonate [31], **AMPS** [32] or acrylic acid (**AA**) [40]. Cationic monomers, monomers that can be protonated or quaternized, e.g. 2-vinylpyridine (**2VP**) [41], 4-vinylpyridine (**4VP**) [41, 42] or **DMAEMA** [43, 44], are available as well. Furthermore, zwitterionic monomers, e.g. **CBMAA-3** [33] or 3-dimethyl(methacryloyloxyethyl) ammonium propane sulfonate (**DMAPS**) [45], have been utilized in RAFT polymerizations. A very frequently employed class of monomers are non-ionic monomers, which are mostly acrylamides, e.g. **AAm** [34], **DMAAm** [34], **DEAAm** [46], **NIPAAm** [47] and *N*-(2-hydroxypropyl)methacrylamide (**HPMA**) [33, 48].

2.1.5 Complex Macromolecular Architectures via RAFT Polymerization

The RAFT process is a tool to generate a broad range of macromolecular architectures (refer to Fig. 2.6). As the structure of the CTA is retained in the formed polymer, a modification of the CTA in the R- or Z-part provides the opportunity to incorporate

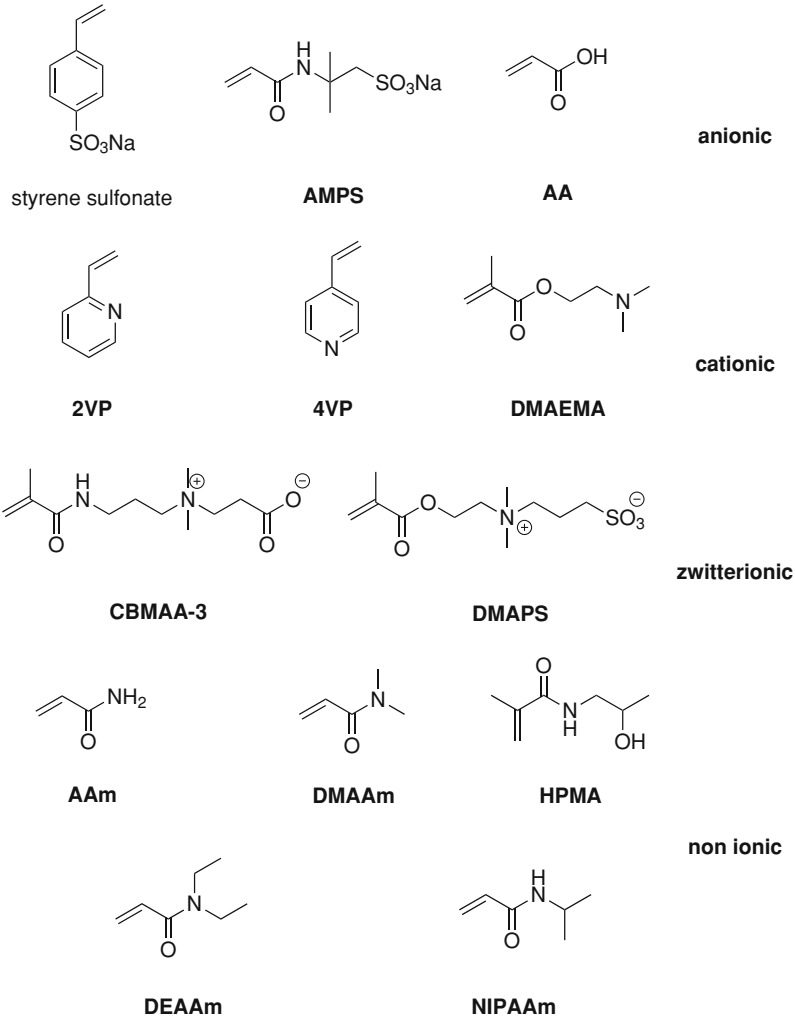


Fig. 2.5 Selection of monomers for the preparation of water-soluble polymers (**AMPS** 2-acrylamido-2-methylpropansulfonic acid; **2VP** 2-vinylpyridine; **4VP** 4-vinylpyridine; **DMAEMA** *N*,*N*-dimethylaminoethyl methacrylate; **CBMAA-3** (3-methacryloylamino-propyl)-(2-carboxy-ethyl)-dimethyl-ammonium (carboxybetaine methacrylamide); **DMAPS** 3-dimethyl(methacryloyloxyethyl) ammonium propane sulfonate; **AAm** acrylamide; **DMAAm** *N*,*N*-dimethylacrylamide; **HPMA** *N*-(2-hydroxypropyl)methacrylamide; **DEAAm** *N*,*N*-diethylacrylamide; **NIPAAm** *N*-isopropylacrylamide)

specific endgroups into polymers [49], e.g. azides [50, 51], alkynes [50], amines [52], alcohols [53] or carboxylic acids [54, 55]. The broad range of possible endgroups leads to a braod range of applications and combinations. Furthermore, several reactive

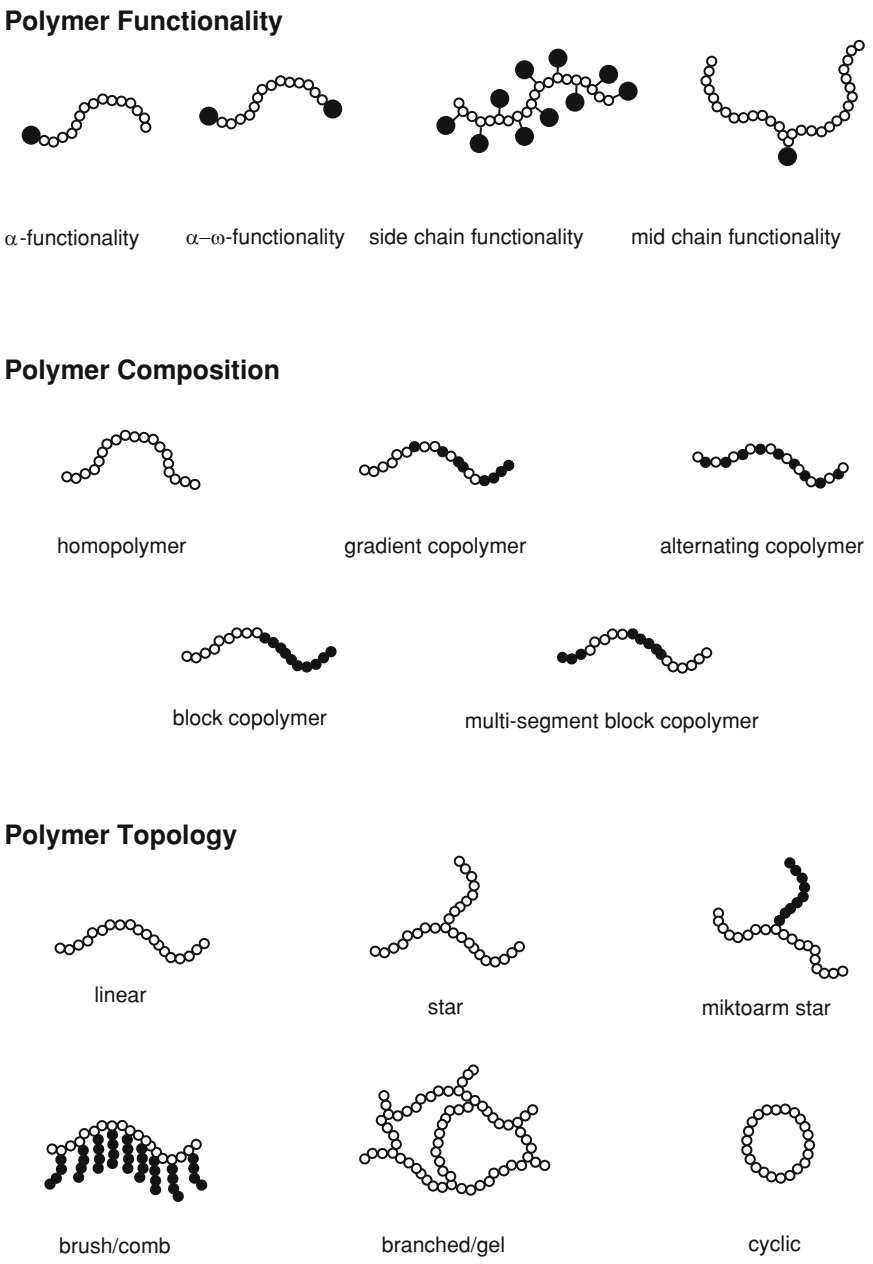


Fig. 2.6 Overview of macromolecular architectures that are accessible via RAFT polymerization

endgroups can be utilized in the formation of complex macromolecular architectures, e.g. in modular ligation reactions [56–59].

An alternative possibility is an endgroup conversion of thiocarbonyl thio endgroups, e.g. thermolysis [60], hydrolysis [61], aminolysis [54] or reduction [62]. Furthermore oxidation [63], radical- [60] and irradiation-induced [64] endgroup removal have been reported in the literature.

Block copolymers can be generated via modular ligation reactions, e.g. CuAAc [49, 50]. Another possibility is the utilization of a macro-CTA, i.e. a polymer that contains a thiocarbonyl thio endgroup. These polymers can be reinitiated and chain extended after initiator and monomer addition [65]. An alternative strategy is the addition of further monomer after high conversion of the first monomer, but in that case gradient block copolymers with tapered transition [17] are obtained [22]. These gradient copolymers are usually not very well suited for microphase separations. A drawback of block copolymer generation via macro-CTAs is that only monomers with similar reactivity can be utilized [49]. A possibility to connect electron rich monomers with electron deficient monomers is the utilization of *N*-(4-pyridinyl)-*N*-methyldithiocarbamate [66]. With this CTA, the formation of block copolymers of methyl methacrylate and vinyl acetate is possible via protonation of the pyridinyl substituent.

Other complex structures can be formed via specially designed CTAs [13, 67], e.g. star polymers [68], polymer brushes [69], dendritic structures [70] or amphiphiles [71].

2.2 Cyclodextrins and Their Complexes

2.2.1 Supramolecular Chemistry

The term of supramolecular chemistry has been defined by Jean-Marie Lehn in 1978. The Nobel laureate of 1987 has defined it as chemistry of non-covalent interactions between host and guest molecules [72, 73]. It can be viewed as chemistry beyond the molecule: While molecular chemistry is based on intramolecular covalent bonds, supramolecular chemistry is based on intermolecular non-covalent bonds [74–76]. Several non-covalent interactions have proven to be versatile in supramolecular chemistry, e.g. hydrogen bonding, metal-ligand interactions or van der Waals interactions [75]. Thus, supramolecular chemistry leads to the formation of supramolecular objects that are defined by the nature of the molecular components and furthermore by the type of interaction between them [75]. In recent years the field of supramolecular chemistry has evolved into areas such as molecular devices and machines or molecular recognition, such as self-assembly and self-organization. One of the frequently utilized host compounds in supramolecular chemistry are CDs that are the focus of the next sections.

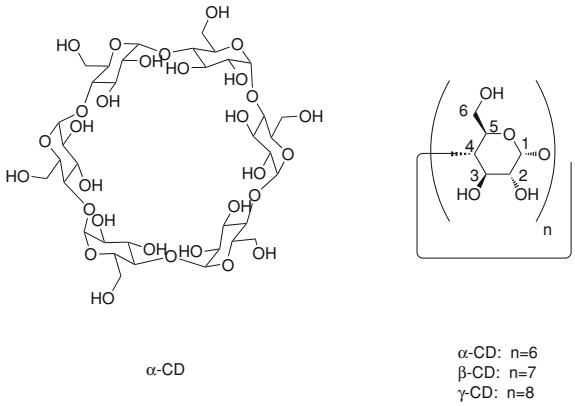


Fig. 2.7 Chemical structure of native CDs and common labelling of C-atoms in the glucose units

2.2.2 Structure and Properties of CDs

CDs are cyclic oligo saccharides of α-D-glucose that are formed through glycosidic α-1,4 bonds [77]. CDs are synthesized in an industrial biochemical process from starch via enzymatic pathways with CD glycosyl transferases, e.g. from *bacillus macerans* [78]. The commonly utilized CDs, also called native CDs, are the ones with n = 6 , 7 or 8 repeating units and are called α-CD, β-CD and γ-CD, respectively (refer to Fig. 2.7 and Table 2.1).

The chemical structure of the CDs resolves in a shallow truncated cone shape of the CD which forms a cavity with openings of two sizes. The exterior of the molecule is very polar/hydrophilic due to many hydroxyl groups whereas the interior is quite nonpolar/hydrophobic. The property of different polarity in different parts of the molecule leads to the most important and utilized ability of CDs: They readily form inclusion complexes with hydrophobic molecules that fit into the cavity in polar environments, mainly in aqueous solution. The complex formation results in several changes of the properties of the guest molecule. First of all, the water solubility of hydrophobic molecules rises significantly. Furthermore, the vapour pressure decreases after complexation as well as the stability against oxidation under air or light induced degradation [79]. In several cases CDs activate chemical reactions, e.g. the hydrolysis of various phenylesters [79, 80]. As CDs are optically active, they are also utilized in chiral catalysis [81]. Other applications include drug delivery [82–84], catalysis [84], chromatography (also for chiral separation) [85] or as food ingredient to mask odours or protect food ingredients against decomposition [84, 86].

CD host/guest complexes can be prepared in solution [87, 88], by coprecipitation [88, 89] or in a slurry [88, 89] as well as in the solid state, e.g. cogrinding or milling [87–89]. In the case of complex formation in solution, sometimes a cosolvent has to be added to enhance the accessibility of the guest, which is depending on the water solubility of the guest molecule.

Table 2.1 Dimensions and water solubility of native CDs

Type of CD	α-CD	β-CD	γ-CD
Number of glucose units	6	7	8
Cavity length (Å)	8	8	8
Approx. cavity diameter (Å)	5.2	6.6	8.4
Water solubility at 25 °C (mol L^{-1})	0.121	0.016	0.168

2.2.3 Thermodynamics and Theory of CD Inclusion Complexation

The complexation of CDs with guest (G) molecules can be considered as a bimolecular process [77]:

$$\begin{aligned} \mathrm{G} + \mathrm{CD} &\rightleftharpoons \mathrm{GCD} \\ \mathrm{GCD} + \mathrm{CD} &\rightleftharpoons \mathrm{GCD_2} \\ \mathrm{GCD} + \mathrm{G} &\rightleftharpoons \mathrm{G_2CD} \end{aligned}$$

These equilibria summarize the formation of CD:G 1:1, 1:2 or 2:1 complexes with the following association constants:

$$K_{11} = \frac{[\mathrm{GCD}]}{[\mathrm{G}][\mathrm{CD}]} \tag{2.9}$$

$$K_{12} = \frac{[\mathrm{GCD_2}]}{[\mathrm{GCD}][\mathrm{CD}]} \tag{2.10}$$

$$K_{21} = \frac{[\mathrm{G_2CD}]}{[\mathrm{G}][\mathrm{GCD}]} \tag{2.11}$$

In general, the formation of more complicated CD host/guest complexes G_mCD_n can be described by the following equilibrium

$$m\mathrm{G} + n\mathrm{CD} \rightleftharpoons \mathrm{G_mCD_n}$$

and equation for the overall association constant β_{mn}:

$$\beta_{mn} = \frac{[\mathrm{G_m}][\mathrm{CD_n}]}{[\mathrm{G}]^m[\mathrm{CD}]^n} \tag{2.12}$$

The driving force for the complex formation is not yet fully understood [77, 87]. Nevertheless, some contributing factors can be identified. The release of water molecules from the cavity leads to an increase in entropy of the system. Furthermore van der Waals interactions and hydrophobic interactions between guest and interior of CD contribute to complex formation. In some cases hydrogen bonding between guest

and the rim of CD takes place. From the temperature dependence of the association constant, enthalpy ($\Delta H_{\text{complex}}$) and entropy ($\Delta S_{\text{complex}}$) of complexation are obtainable [79]. In most cases, $\Delta H_{\text{complex}}$ is negative which leads to complex dissociation at higher temperatures [77, 88, 90, 91], whereas $\Delta S_{\text{complex}}$ can have negative or positive values depending on the interactions that take place during complexation. In the complex formation several steps have to be considered [79, 92]:

1. The guest molecule has to approach the CD
2. Enthalpy rich water molecules have to be released from the cavity (results in a rising entropy of the system)
3. The hydration shell of the guest has to be removed at least partly
4. Interactions (mostly weak van der Waals attractions) of the guest molecule with the rim of the CD and the inside (the guest molecule enters the cavity)
5. Possible formation of hydrogen bonds between CD and guest
6. Re-formation of the hydration shell of exposed parts of the guest molecule and around the CD molecule

From the point of complex formation kinetics in steps 1, 4 and 5 the size of the guest molecule plays an important role and no complex formation is observed for guests that extend the cavity size. The assembly of water molecules relies on several factors, e.g. pH value or ionic strength, which is independent from the respective guest molecule. Most likely steps 3 and 4 can be considered rate determining [92]. The size of the guest group is not only a criterion whether it is possible for the guest to enter but also for the stability of the complex. As the interactions between CD and guest are rather weak and of a short range, the complex stability depends strongly on a good fit between CD and guest. In some cases a weak fit between CD and guest can be compensated with the formation of different complex geometries/stoichiometries (refer to Sect. 2.2.4).

2.2.4 Complex Types, Common Host/Guest Pairs and Their Stability

From the geometry of CD two complexation modes are possible. Depending of the dimension of the guest, it can enter the cavity from the primary or the secondary side of CD (refer to Fig. 2.8). The primary side is on the face of C6 and OH-6 and has a slightly smaller opening. The secondary side is on the face of C2 and C3 with a slightly larger opening of the cavity. Complexes with different complexation modes can be identified via multi dimensional NMR spectroscopy [93] and X-ray crystallography [77, 94–96]. Furthermore, different complex stoichiometries are possible [84]. The most common cases are 1:1 CD/guest complexes but 2:1 and 1:2 are described as well, e.g. the complex 1-bromoadamantane with 2 α-CD molecules [97] or the complex of γ-CD with 2 pyrene molecules [98, 99]. The complex stoichiometry can be identified via the method of continuous variation, i.e. Job's plot [93, 97, 100]. In this analysis the product of mole fraction and complexation induced change in the chemical shift

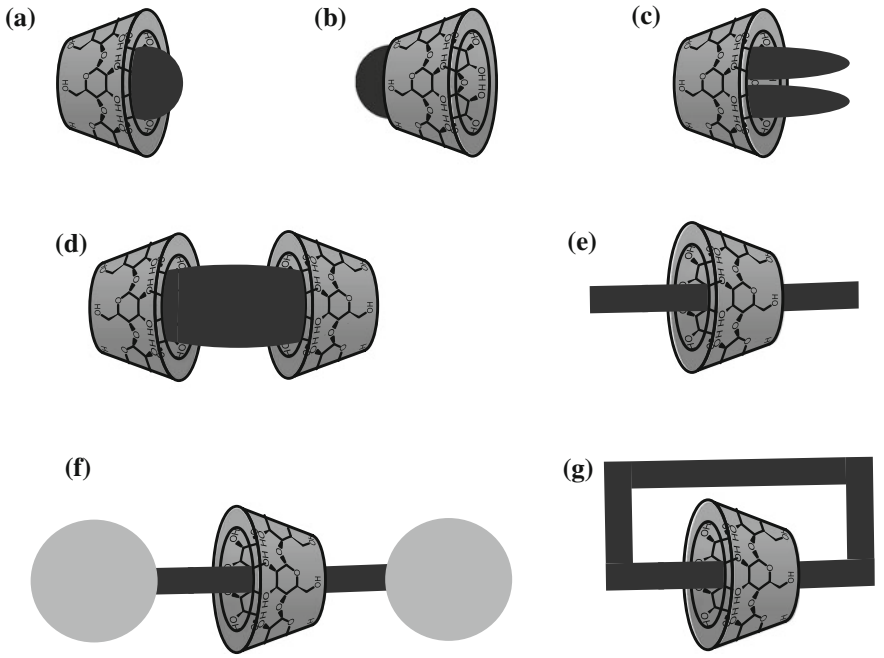


Fig. 2.8 Different types of complexation: **a** 1:1 CD/guest complex from the secondary side, **b** 1:1 CD/guest complex from the primary side, **c** 1:2 CD/guest complex, **d** 2:1 CD/guest complex, **e** pseudo rotaxane, **f** rotaxane, and **g** catenane

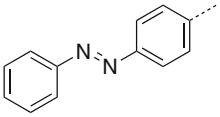
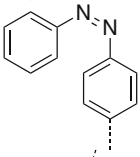
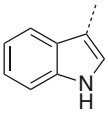
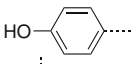
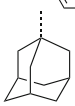
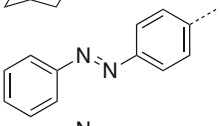
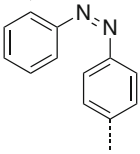
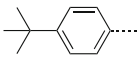
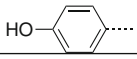
in the NMR spectrum is plotted against the mole fraction of guest or CD. The position of the maximum of the obtained curve indicates the complex stoichiometry.

CD complexes with axial shaped guests are called pseudo rotaxanes if they are not fixed via stopper groups (refer to Fig. 2.8) [101]. After fixation with large stopper molecules that suppress the dethreading of CD, complexes of CD with axial guests are called rotaxanes [101, 102]. In that case the CD complexation loses its reversibility and the formed bond between host and guest is a mechanical bond. Another class of mechanically interlocked molecules are catenanes, which are the connection of two or more rings via intertwining (Fig. 2.8) [103].

The different complex types can be transferred to polymers as well, e.g. in poly pseudo rotaxanes [104, 105], polyrotaxanes [106], side chain pseudo polyrotaxanes [107], side chain polyrotaxanes [108] or pseudo rotaxane star polymers [109, 110]. Rotaxane formation can be utilized, e.g. for the formation of supramolecular polymers [111] or hydrogels [112]. The concept of mechanical bonds was utilized for example in the synthesis of mechanically interlocked block copolymers [113, 114].

While the complex stoichiometry can be addressed via Job's plot, the association constant, and thus an equivalent for the complex stability, is accessible via isothermal titration calorimetry [115] or the Benesi-Hildebrand plot [116–118] for instance. In isothermal titration calorimetry the evolution of heat is measured during the addition of guest or host to a host or guest solution, respectively. A fit of the plot of

Table 2.2 Common guests for the native CDs and the respective association constants

Guest	Structure	Type of CD	log β (log M^{-1})
trans-Azobenzene		α	4.0 [119]
cis-Azobenzene		α	0.6 [120]
Indole		α	7.8 [121]
Phenol		α	4.2 [121]
Adamantyl		β	4.6 [122]
trans-Azobenzene		β	2.7 [123]
cis-Azobenzene		β	0.4 [123]
tert-Butyl phenyl		β	4.4 [124]
Phenol		β	3.4 [121]

molar ratio against enthalpy leads to $\Delta G_{\text{complex}}$ and thus the association constant can be derived, while the surface under the curve gives the complexation enthalpy $\Delta H_{\text{complex}}$. The utilization of the Benesi-Hildebrand plot gives the opportunity to obtain association constants via changes of absorption in UV spectra or the chemical shift in NMR spectra.

Table 2.2 shows a selection of different guests with the respective association constant. For, α-CD mono or *para* substituted aromatic structures are commonly utilized, e.g. phenyl or azobenzene with association constants up to 10^4 M^{-1}, as well as aliphatic chains or poly(ethyleneglycol) (PEG). One of the strongest associations are reported between α-CD and indole with an association constant of 10^7 M^{-1} probably due to the formation of additional hydrogen bonds. The adamantyl-group

is a well-known guest group for β-CD with association constants up to 10^5 M^{-1}. Azobenzene and *tert*-butyl phenyl are also utilized in several examples. In the case of γ-CD, very bulky guests are necessary, e.g. two pyrene molecules or cyclododecane.

2.3 Complex Macromolecular Architectures Governed by CD Complexes

In recent years CD complexes have proven to be a perfect tool for the generation of complex macromolecular architectures. Almost every conceivable architecture has been described so far. Especially the development of controlled radical polymerization techniques for the synthesis of endfunctionalized polymers had a very significant impact on the research in this area.

Figure 2.9 shows a compilation of different architectures that were generated via CD host/guest complexes so far. CDs have been utilized for the modification of polymer functionality, polymer composition and polymer topology. CD functionalized polymers are rather readily accessible via living/controlled radical polymerization giving control of end chain and mid chain functionality. Diverse supramolecular polymer compositions can be obtained via incorporation of CD complexes at the interface between different blocks. To achieve more complex topologies, a combination of different functionalized building blocks is necessary, e.g. multi CD functionalized polymer strands. In general, the control over polymer functionality gives rise to the formation of complex supramolecular polymer compositions and topologies.

2.3.1 Common CD Containing Building Blocks

Although CDs possess a large number of functional groups, the reactivity of the primary and secondary hydroxyl groups differs significantly, which gives the opportunity to exclude some of the hydroxyl groups in specific reactions [125, 126]. Nevertheless, at least 6 hydroxyl groups with the same reactivity exist in a CD molecule. To obtain mono functionalization, the reaction conditions have to be monitored carefully. The most commonly used intermediate is the mono tosylate at C6, which can be synthesized in pyridine for all native CDs [127–129] or in aqueous NaOH solution for β-CD and α-CD [130, 131]. The tosylate can be transformed into several useful building blocks, e.g. azide [128, 129], thiol [132] or amine via nucleophilic substitution with a diamine [133]. The azide is available via a nucleophilic substitution of the tosylate with sodium azide [128, 129, 131], whereas the thiol is formed via a nucleophilic substitution with thiourea and subsequent hydrolysis [132, 134]. The azide can be further converted into an amine via reduction [127–129]. With these 3 substituents a large variety of modern polymer conjugation reactions can be utilized, e.g. CuAAc [130, 135] and thiol-ene reactions [136]. CD-functionalized

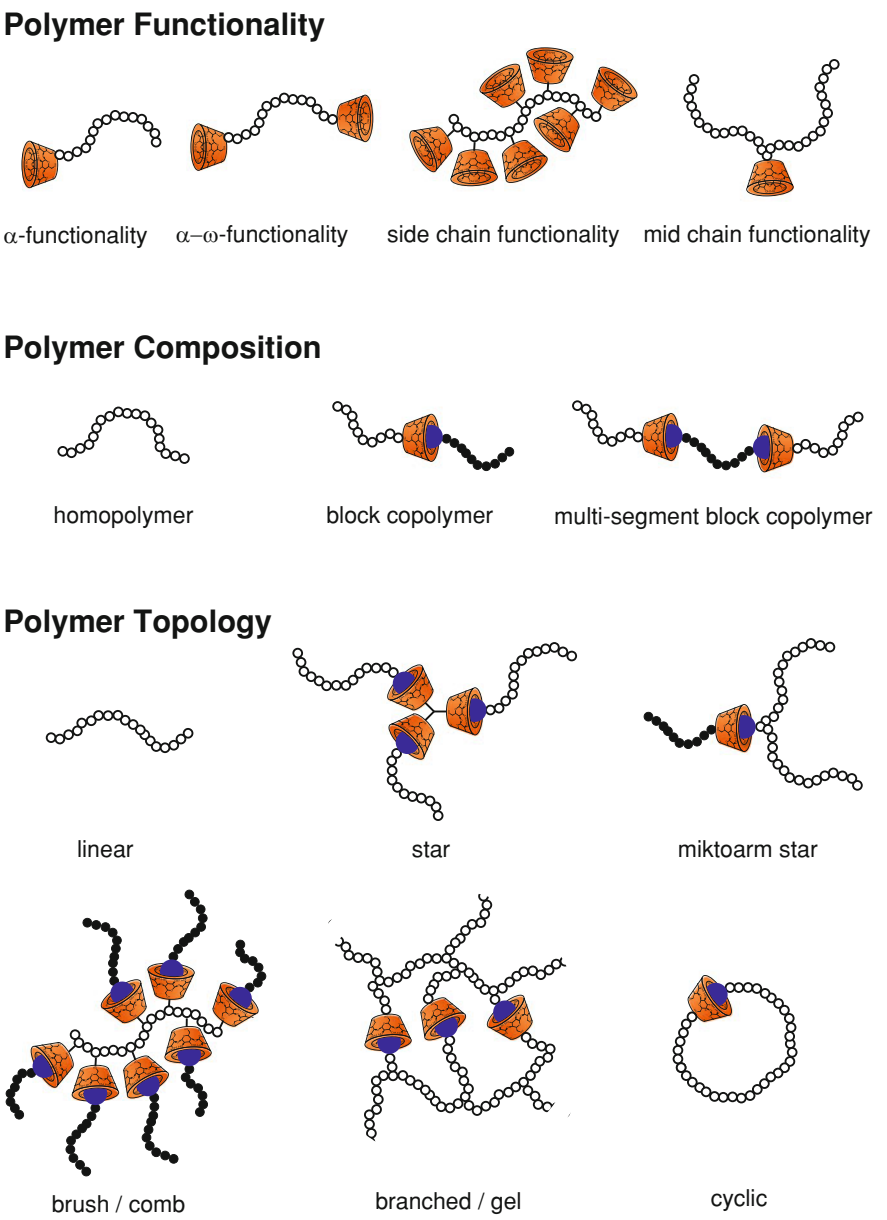


Fig. 2.9 Complex macromolecular architectures via CD-driven supramolecular complexation and macromolecular building blocks with CD moieties (CD is depicted in *orange*; guest groups are depicted in *blue*)

polymerization mediators, e.g. for NMP [137], ATRP [138] or RAFT [139] have been described in the literature as well as post-polymerization conjugation reactions with CDs [138, 140]. Mono functionalizations at C2 are described in the literature as well [141, 142], yet C2 or C3 derivatives are not utilized as frequent as the C6 derivatives. Certainly an esterification of the hydroxyl groups is possible as well, yet the selectivities are usually low. Either full conversions are initially targeted or lower substitution grades are targeted and the obtained mixtures have to be purified in inconvenient procedures.

2.3.2 Block Copolymers

The formation of block copolymers via CD complexes is mainly restricted to AB diblock copolymers so far. Almost exclusively β-CD has been utilized in that regard. The synthesis of supramolecular diblock copolymers is straight forward as only two components are needed: a CD-functionalized polymer and a guest functionalized polymer. These building blocks are commonly obtained via controlled radical polymerization techniques yet in some cases cationic or anionic polymerization have been utilized as well.

One of the first examples is an AB diblock copolymer of PNIPAAm and P4VP synthesized via RAFT polymerization by Zhang and coworkers that has proven to be pH and thermoresponsive [143]. This block copolymer was exploited in temperature- and pH-induced micellization and vesicle formation which was observed via DLS, SLS, fluorescence measurements and TEM. At a pH value over 4.8 and a temperature of 25 °C vesicles were formed and at a pH value of 2.5 and a temperature of 60 °C micelles were formed. Another example of double stimuli responsive block copolymers, i.e. with schizophrenic behavior, has been described by Liu et al. [138]. Again pH- and thermoresponsive behaviour was combined but this time via PDMAEMA and PNIPAAm blocks synthesized via ATRP. Vesicle formation was observed at low pH values and high temperatures (pH 4 and 50 °C), whereas micelles were formed at high pH values and low temperatures (pH 9 and 25 °C), which was proven via TEM, DLS and SLS. Voit and coworkers described a supramolecular diblock copolymer consisting of PNIPAAm synthesized via ATRP and poly(2-methyl-2-oxazoline) synthesized via cationic ring-opening polymerization [144]. The temperature-responsive PNIPAAm block was utilized for temperature-induced aggregation. These examples evidence the impact that CD-based supramolecular chemistry can have in the area of macromolecular architectures.

CD complexes provide another possibility for stimuli response. Not only different polymer types can be utilized in the area of stimuli-responsive materials, yet the supramolecular connection is addressable via external stimuli as well. One of the first examples is the utilization of a voltage responsive connection via a ferrocene endgroup which was described by Yan et al. [145]. A β-CD functionalized PSty and a ferrocene functionalized PEG were utilized. The connection between the blocks can be disrupted, as ferrocene molecules can be oxidized reversibly and the ferrocene

cation does not fit into the β-CD cavity. At first, block copolymer vesicles were obtained that dissociated upon application of an electric current. The rate of dissociation and the release of a test molecule could be adjusted via the amount of the voltage. Another example of diblock copolymers with stimuli responsive linkage was described by the same group [146]. Supramolecular based nanotubes were formed (length ~220 nm and diameter ~90 nm) via a supramolecular poly(ϵ-caprolactone-*b*-AA) (PCL-*b*-PAA) diblock copolymer. The supramolecular complex was formed between azobenzene and α-CD that leads to a light responsive linkage between the blocks. Furthermore, the nanotubes were loaded with Rhodamine B that could be released via light induced disassembly of the nanotubes. Stenzel and coworkers prepared supramolecular core shell nanoparticles with a PMMA core and poly(hydroxy ethylacrylate) (PHEA) shell [136]. The guest functionalized PHEA building block was obtained directly via RAFT polymerization, whereas the CD functionalized PMMA block was obtained via RAFT polymerization of MMA, a Chugaev thermolytic endgroup conversion and a subsequent thiol-ene reaction with mono thiol functionalized β-CD. Core shell nanoparticles (diameter ~150 nm) were obtained after mixing of the building blocks in DMF and subsequent water addition or by the generation of core PMMA nanoparticles in water and addition of the water soluble building blocks. The addition of free β-CD led to the disassembly of the complexes and aggregation of the water insoluble blocks. Recently Yuan and coworkers described a biodegradable diblock copolymer of P(lactide) (PLA) and PEG with a β-CD and ferrocene governed connection [147]. Cyclovoltammetry was utilized to study the redox response of the block copolymer. Furthermore micelles were formed and characterized via TEM and DLS. Cytotoxity and drug-release was investigated with regard to the redox stimulus as well. A block copolymer with pH-responsive supramolecular linkage between β-CD and benzimidazole was described by Zhang et al. [148]. Thus, a diblock copolymer of PCL and dextran was synthesized and supramolecular micelles were formed. The micelles were utilized for in vitro doxorubicin delivery that was supported by the difference of intra and extracelluar pH.

A diblock copolymer with a special linking moiety was described by Quan et al. [130]. In this case a dilinker consisting of α-CD and β-CD connected with a short spacer was utilized to form a diblock copolymer of PNIPAAm and PCL. Furthermore, cell targeting ligands were introduced to enhance cell uptake efficacy. To protect the formed core shell nano-sized assemblies in body fluids, PEG moieties were incorporated as well. The formed assemblies were utilized in drug delivery experiments that showed tumor-triggered release of loaded molecules. This particular example shows how powerful CD complexes are as a tool for the formation of macromolecular architectures with regard to the specific application, e.g. drug delivery [130] or the formation of nano objects [145, 146]. Especially the stimuli-responsive nature of several CD/guest pairs gives the opportunity to disassemble the block copolymer at the junction of the different blocks. Thus, the distinct properties of block copolymers can be utilized but with the additional property of disassembling the blocks. This concept has been utilized recently by Hawker and coworkers in block copolymer lithography with block copolymers that are coupled via hydrogen bonds. This

example shows that supramolecular bonded block copolymers can indeed mimick the behavior of their covalent analogues [149].

2.3.3 Brush Polymers

The synthesis of supramolecular brush polymers can be conducted via two pathways. Either CD molecules are connected to a backbone or surface and a guest endfunctionalized polymer is added or guest molecules are connected to a polymer backbone or surface and CD-endfunctionalized polymers are added. The forming complexes lead to brush-like architectures. Of course the complex formation is governed by equilibria and thus the obtained grafting density strongly depends on the association constants. Furthermore, steric factors play an important role as CDs have a very bulky structure that can suppress high grafting densities.

A supramolecular brush formation in solution has been described by Bernard et al. [140]. A CD-containing backbone was synthesized in a two step procedure. Firstly, trimethyl silyl protected propargyl methacrylate was polymerized via RAFT, subsequently the terminal alkyne groups were deprotected and conjugated with β-CD-N_3 in a CuAAc reaction. Short PAA chains endfunctionalized with an adamantyl-group were synthesized and brushes were formed in aqueous solution. The brush formation was proven via DLS and NOESY (nuclear Overhauser enhancement spectroscopy). Although a dodecyl functional RAFT agent was utilized, no competing complex formation was evident, which was proven via comparison of dodecyl-functional chains with chains after RAFT endgroup removal. Jiang and coworkers presented a supramolecular brush with a copolymer of *N*-vinylpyrolidone and a CD functional monomer and doubly adamantyl endfunctionalized PCL [150]. Interestingly, micellar aggregates were obtained, as shown by TEM and DLS, and no gel formation was observed, although a doubly guest functional polymer was utilized. Later Zhang and coworkers presented a supramolecular brush consisting of a CD-functionalized polymer backbone and adamantyl functionalized oligo ethylene glycol dendrons. The thermoresponsive behavior was studied as a function of several factors, e.g. dendrimer generation or hydrophobicity of the dendrimer endgroups [151]. In that way the LCST could be tuned from 34 to 56 °C. It was found that the dehydration and collapse of the oligo ethylene glycol chains leads to disassembly of the host/guest complexes, which was studied via NMR and ITC. Frey and coworkers investigated the binding strength of PHPMA featuring pendant β-CD functionalities with adamantyl-functionalized hyperbranched and linear poly(glycerols) as well as their block copolymers with PEG [152]. The complex formation was monitored via diffusion-ordered NMR spectroscopy (DOSY), ITC and fluorescence correlation spectroscopy. The steric effect of the hyperbranched grafts resulted in decreased association constants, while the incorporation of PEG spacers led to more stable complexes. Very recently Hetzer et al. [153] showed a supramolecular brush formation of CD end-functionalized PDEAAm with a copolymer consisting of DMAAm and a phenolphthalein-functionalized acrylamide. Due to the complex formation with the

dye functionalized side-chains a color change in the solution was observable during complexation. Another stimuli responsive supramolecular brush polymer was described by Yuan et al. [154]. PEG-*b*-P(glycidyl methacrylate) was prepared via RAFT polymerization and the glycidyl containing block was decorated with β-CD. Addition of a ferrocene endfunctionalized PCL led to the formation of supramolecular brushes that showed redox responsive brush formation coupled with redox responsive micelle formation.

Apart from solution studies several reports regarding surface brushes exist in the literature. Li and coworkers studied the grafting of doubly adamantyl endfunctionalized polymers on CD modified cellulose [155]. After the formation of the supramolecular complexes the grafting was proven via XPS, ellipsometry, TGA and FT-IR. Thus, a supramolecular grafting on the renewable resource cellulose was achieved. Reinhoudt and Huskens introduced the concept of molecular printboards, i.e. mono layers of CD host molecules on a planar surface that are capable of the stable attachment of guest molecules [156]. This concept has been exploited to generate different grafted structures, e.g. on gold [156] or SiO_2 [157]. Furthermore, patterns on the surface have been generated via micro contact printing [157–159]. These molecular printboards have been utilized to immobilize proteins [160, 161], fluorescent dyes [159] or Eu^{3+} luminescent complexes [158]. A similar approach was utilized to graft an azobenzene functionalized cell recognition peptide onto an α-CD functionalized gold surface that showed reversible and photocontrolable cell attachment [162].

2.3.4 Star Polymers

CD-based star polymers can be divided into two categories. Star polymers with CD as a core moiety due to its high concentration of functionality, which is the most frequent utilization of CDs for star polymers. The other possibility is to utilize host/guest complexes to obtain supramolecular star polymers, e.g. via a core molecule with several CD moieties and guest functionalized polymers.

One of the first reports of CD-centered stars is from the work of Haddleton and coworkers, where a 21 arm star polymer consisting of PMMA or PSty arms was synthesized via ATRP with a grafting-from approach [163]. Furthermore, block copolymer stars were formed from the obtained macro initiators. A similiar approach was conducted by Stenzel et al., who described a CD-centered 18 arm PSty star synthesized via living radical polymerization mediated by a half-metallocene iron carbonyl complex [164] and a CD-centered 7 arm star formed via RAFT polymerization of Sty [26, 165], as well as block copolymers with ethyl acrylate [165]. The range of utilized monomers for the arm-forming polymers was subsequently extended later to *tert*-butyl acrylate [166], oligo ethyleneimine [167], azobenzene monomers [168], 2-ethyl-2-oxazoline [169], glycomonomers [170], HEA [170], NIPAAm [171], PNIPAAm-*b*-PDMAAm [172], PS-*b*-P(3-hexylthiophene) [173] and P(L-lysine) dendrons [174] by several research groups. Kakuchi and coworkers

utilized mono amino β-CD to attach a NMP initiator, followed by a living/controlled radical polymerization of Sty [175]. The remaining hydroxyl groups were utilized to attach ATRP initiator via esterification and subsequently MAA or *tert*-butyl acrylate was polymerized to form a CD centered miktoarm structure. Recently Haddleton and coworkers introduced 7 thiols on the secondary face of β-CD for subsequent thiol-ene reactions, e.g. with oligo ethylene glycol methacrylate (OEGMA), and utilized the remaining 14 hydroxyl functions as initiator for the ring-opening polymerization of CL, which leads to the formation of a CD-centered miktoarm star polymer [176]. These examples are of particular interest because the different reactivities of the β-CD hydroxyl groups were utilized to generate a complex macromolecular architecture. A different asymmetric β-CD based star architecture has been described recently by Liu et al. [177]. The primary face of CD was grafted with PDMAEMA, while the secondary face was utilized to attach a magnetic resonance imaging contrast agent. The poly-cationic PDMAEMA was subsequently used to promote polyplex formation with plasmid DNA. Finally in vitro DNA delivery, cytotoxity and magnetic resonance imaging was probed. Moreover, another asymmetric β-CD based star architecture was described by Shen et al. [178]. While the primary face was decorated with PEG, the secondary face of β-CD was grafted with 2-[(methacryloyl)oxy]ethyl acrylate / cysteamine dendrimers that showed the formation of well-defined aggregates in aqueous solution. A γ-CD centered oligo ethyleneimine star was prepared by Li et al. [179]. The γ-CD core was utilized to encapsulate the drug paclitaxel. Furthermore a cell targeting ligand was attached and a polyplex was formed with plasmid DNA. Finally cell viability and gene transfection efficiency were studied. A dumbell-shaped architecture containing of two β-CD centered PNIPAAm stars connected covalently via a PEG backbone was described by Zhang et al. [180]. The thermoresponsive characteristics were studied showing the formation of flower like micelles. An alternative architecture involving CD-core star polymers has been published recently by Wenz and coworkers which is a combination of rotaxane and star architectures [181]. Here α-CD centered PMMA stars were threaded onto a PEG backbone and fixed via large stopper molecules. PMMA chains were grafted from ATRP initiators connected to the threaded α-CD moieties on the rotaxane and were characterized via DOSY, SEC and AFM. An interesting feature of the thus formed brushes is their sensitivity to mechanical forces during SEC measurement, which led to the scission of the PEG thread. A similar approach was followed by Nagahama et al. [182]. PEG was threaded with α-CD to form a polyrotaxane. The remaining hydroxyl groups of the α-CD threads were utilized to grow PLA. Continuous anisotropic phases were formed in the bulk state. The crystallization behavior was studied via DSC, X-ray diffraction and polarized optical microscopy. An accelerated stereo complex formation was found that was attributed to the enhanced moveability due to the rotaxane structure.

Fewer reports are in the literature on star architectures governed by host/guest complexes. An interesting architecture in that regard is the connection of two CD-centered stars with a doubly guest functional polymer, which leads to a dumbbell shape in solution that has been described in two studies [183, 184]. In the first report β-CD centered PNIPAAm with 4 arms was connected with a doubly adamantyl

functionalized PEG, the complex formation was proven via NOESY and the change in the LCST was monitored depending on host/guest ratio or the molecular weight of the employed PEG [183]. Later, β-CD centered PNIPAAm was connected with a doubly adamantyl functionalized poly(propylene glycol) (PPG) [184]. As this system contains two thermoresponsive polymer types, the aggregation behavior was studied depending on the temperature via DLS, NMR, fluorescence measurements, AFM and TEM. The formation of supramolecular block copolymers was evident in cold water, whereas micelle formation was observed at temperatures over 8 °C and above 22 °C micelle destabilization was observed. A similar structure was described by Allcock et al. [185]. A β-CD centered POEGMA star was complexed with an adamantyl endfunctionalized P(bis-(trifluoroethoxy)phosphazene). The formation of micelles was monitored via DLS, TEM and AFM. Furthermore β-CD moieties were introduced into P(phosphazene) side-chains to obtain multiple β-CD grafted polymers. Multiple adamantyl functionalized P(phosphazene)s were prepared as well ans finally the gelation behavior was studied. The formation of an ABC miktoarm star polymer was published recently by Zhu and coworkers that required several functionalization reaction with β-CD [135]. In brief, β-CD was mono tosylated, converted into the azide and mono tosylated again. PEG was conjugated via CuAAc, the remaining tosylate was converted into the azide and subsequently an ATRP initiator was added via CuAAc. DMAEMA was polymerized via ATRP to obtain a miktoarm star with two different arms. A third arm consisting of adamantyl functional PMMA was connected via supramolecular complex formation. Due to the hydrophobic character of PMMA, micelles were obtained in solution and characterized via DLS and TEM. Wu and coworkers utilized a threefold β-CD core to connect three guest functionalized oligo ethylene glycol dendrimer arms [186]. The thermoresponsive behavior of the formed dendrimer stars was investigated showing a variation in the LCST from 43 to 72 °C depending on dendrimer generation, dendrimer endgroup (ethyl or methyl) and ratio of different dendrimer types (with ethyl or methyl endgroup). Furthermore, the effect of salt concentration was investigated as well as the thermally induced decomposition of the supramolecular complexes. An interesting combination of CD-based host/guest chemistry and a protein (concavalin A (ConA))/mannopyranoside interaction was shown by Chen et al. [148]. An α-mannopyranoside and β-CD functionalized dilinker was synthesized and subsequently the supramolecular recognition was probed via ITC. An association constant of 8.4×10^3 M^{-1} was found for the ConA dilinker complex. Addition of adamantyl functionalized PEG showed a further recognition of the β-CD moiety and the adamantyl group with an association constant of 1.1×10^5 M^{-1}. The complex formation was additionally investigated via DLS and SEC evidencing a strong dependence of the number of attached PEG chains on the concentration of the solution. Addition of free α-CD molecules lead to hydrogel formation via a supramolecular interaction of the PEG chains and α-CD. Recently Schmidt et al. showed the formation of supramolecular X- and H-shape star block copolymers. The complex formation was investigated via DLS, NOESY and turbidimetry. Additionally, the temperature induced aggregation behavior was studied via temperature sequenced DLS measurements. A similar aggregation and micelle

destabilization behavior as in the earlier described dumbbell shaped aggregates was found [184].

Jiang and coworkers utilized host guest complexes to form brush-like star architectures with different spherical cores, e.g. SiO_2 nanoparticles [187], CdS quantum dots [188, 189] or gold [190]. In the case of SiO_2 nanoparticles, PEG arms were utilized and subsequently α-CD was added to induce hydrogel formation. In another work quantum dots were utilized as a core for azobenzene or ferrocene endfunctionalized PDMAAm-*b*-PNIPAAm block copolymers [188, 189]. The thermoresponsive nature of the PNIPAAm blocks was utilized to induce hydrogel formation above the LCST. The hydrogels showed a variation of photoluminescence depending on the temperature and thus the gel formation, which can be attributed to the confinement of the quantum dots in the gel. Furthermore, UV-light and electrochemical response was probed. CD-functionalized gold nanoparticles were grafted with azobenzene endfunctionalized PNIPAAm-*b*-PDMAAm, which gave the opportunity to disrupt the supramolecular complex upon UV-irradiation [190]. Heating above the LCST of the PNIPAAm block led to the formation of vesicles. A similar approach was described earlier [191]. In this case gold nanoparticle cores with α-CD shell were utilized as well. Azobenzene endfunctionalized PNIPAAm homopolymer was supramolecularly attached. Subsequently the photoresponsive behavior and the thermal behavior of the aggregates were studied in detail.

2.3.5 Branched Polymers and Gels

The probably most intensively studied field in CD driven macromolecular architectures is the formation of branched structures and hydrogels. Several reviews based on these materials can be found elsewhere [192–196]. Nevertheless, in this section a short overview on polymeric CD-based hydrogels and branched structures that have been synthesized via controlled radical polymerization is presented. In general, the formation of branched structures and hydrogels can be conducted via different pathways. A large amount of host and/or guest functionalities can be incorporated into the side chain of the polymers or as endgroup to induce supramolecular crosslinking. Furthermore, single CD molecules can be utilized as crosslinkers if the guest group is small and two guests can be included, which leads to single-CD crosslinking points. Alternatively CDs can act as crosslinker via aggregation/crystallization.

An example of the latter category utilizes OEGMA based polymers with side chains of POEGMA as a double brush structure that was formed via ATRP. The formation of a hydrogel was induced via addition of α-CD [107]. Interestingly, the formation of hexagonal crystals was observed in the hydrogel which is due to the formation of columnar microcrystalline domains of α-CD. Later P(EG-*co*-DMAEMA) brushes were utilized to form thermo- and pH-responsive gels after α-CD addition [197]. The gelation behavior was altered via copolymer concentration, pH value, PEG branch density and the chain uniformity of the copolymers. With these gels drug release at different pH values and temperatures was studied. The same crosslinking

method was employed with PEG-*b*-PDMAEMA block copolymers, which lead to a series of different microgel morphologies depending on pH value or ionic strength, e.g. hexagonal, bowl or spherical structures that could be visualized via TEM [198]. A recent utilization of α-CD based crosslinking via a poly pseudo rotaxane formation is the supramolecular anchoring of DNA polyplexes in hydrogels formed from PEG-*b*-PCL-*b*-PDMAEMA block copolymers and α-CD [199]. The polymers were synthesized via a combination of ATRP and ring-opening polymerization. Subsequently, DNA polyplexes were formed from blockcopolymer micelles and plasmid DNA. The addition of free PEG chains and α-CD leads to hydrogel formation. The following studies on the release of the incorporated DNA showed sustained release of stable polyplexes with high bioactivity. Yuan and coworkers synthesized a PCL-*b*-POEGMA with pyrene endgroup via a combination of ROP and ATRP [200]. The amphiphilic block copolymer was assembled into micelles and α-CD was added to obtain gelation. Viscoelastic behavior, temperature response and in vivo drug-release were studied with these gels. Furthermore Ji and coworkers described a PEG-*b*-PNIPAAm block copolymer that was utilized to form micelles in solution via heating above the LCST of the PNIPAAm block [201]. Moreover α-CD was added at ambient temperature to induce crystallization due to interactions with the PEG blocks leading to reverse micelles.

A β-CD centered star polymer of PDMAEMA was protonated and utilized to form networks with polyanionic PAA-*b*-PEG di- and triblock copolymers [202]. Depending on the structure of the polyanionic block, fibrillar or spherical microstructured gels were obtained. SEM, TEM, DLS and rheological measurements were carried out to study the obtained materials. Furthermore, the remaining cavity in the β-CD moiety was utilized to include a model drug and study the release behavior. Another example is the temperature induced formation of PNIPAAm hydrogels from a β-CD centered PNIPAAm-*b*-PDMAAm three arm star polymer [172]. Again, the β-CD cavity was utilized for small molecule release. As described before in Sect. 2.3.4, quantum dot centered hydrogels formed due to the LCST of PNIPAAm blocks have been generated as well [188, 189].

Kang and coworkers presented the synthesis of a doubly β-CD functionalized poly(2-(methacryloyloxy)ethyl succinate) via RAFT polymerization [139]. This polymer was utilized in the formation of poly pseudo rotaxanes with an acrylate endfunctionalized PEG-*b*-PPG-*b*-PEG. The acrylate functions were subsequently reacted in a thiol-ene reaction with a multifunctional thiol to form permanent crosslinking points. Thus, a sliding hydrogel was obtained evidencing pH response (from the succinate) and thermoresponse (from the PEG and PPG blocks). Swelling ratios and thermal properties could be adjusted via different chain lengths of the β-CD functionalized polymer which is rather easy via changing the conditions of the RAFT polymerization. Recently Hetzer et al. [203] showed the network formation of a doubly adamantyl functionalized PDMAAm and a three-fold β-CD functionalized linker molecule. Rheological investigations showed increasing viscosities depending on CD/guest ratio, chain length and concentration. Furthermore the viscosity could be reduced drastically via addition of free CD molecules or free guest molecules. Zhang et al. [204] described a redox sensitive network utilizing two- or three-fold β-CD

linker molecules and three- or four-fold ferrocene-functionalized P(ethylene imine). The formed material was analyzed via 2D correlation FT-IR spectroscopy and measurements of the mechanical material properties. Furthermore the addition of oxidants led to dissolution of the material. A redox responsive hydrogel was described by Yuan et al. [205]. DMAAm-based β-CD and ferrocene-containing polymers were formed via RAFT polymerization. A mixture of both polymer types gave a hydrogel that proved to be redox responsive. A photoresponsive hydrogel based on β-CD and azobenzene interactions was described by Guan et al. [206]. A copolymer of NIPAAm and an azobenzene monomer was interacted with a difunctional β-CD containing molecule that has a disulfide connection between the CD moieties. Double stimuli responsive gels were obtained. The azobenzene guest groups allowed for photoresponsive sol-gel transition, where as the disulfide bonds facilitated redox responsive sol-gel transition. Moreover, Gao and coworkers prepared a P(glycidyl methacrylate) via ATRP that was subsequently transformed with diethylenediamine to obtain amine functional polymers [207]. Afterwards β-CD was introduced and complexes with insulin formed. Finally in vitro release of insulin was probed that increased upon addition of competing guests.

2.3.6 Other Architectures

Jiang and coworkers presented a block copolymer-like structure consisting of Frechét-type benzyl ether dendrons (generations 1, 2, and 3) with an azobenzene at the apex and a β-CD functionalized PNIPAAm [208]. These supramolecular block copolymer amphiphiles formed vesicles or micelles in aqueous solution depending on dendron generation. Furthermore, UV-irradiation lead to the disassembly and formation of irregular particles which could be reversed via irradiation of visible light. Heating above the LCST of the PNIPAAm block leads to reversible aggregation of the particles. Vesicles of a doubly CD endfunctionalized P(ether imide) were prepared by Guo et al. [209]. β-CD cavities were present on the inner and outer walls of the vesicle that could be addressed via guest functionalized PEGs depending on the molecular weight, e.g. with 1 and 2 k PEG inner and outer surface was modified, whereas with 5 k PEG the inner surface was modified only partially. Giacomelli et al. [137] formed PSty centered micelles with β-CD surface. The underlying β-CD functionalized PSty was prepared via NMP. The formation of a supramolecular cyclic polymer was described by Inoue et al. [210]. A PEG with azobenzene and β-CD endgroup was utilized in that regard. The formation of cycles could be performed in high dilution, whereas intermolecular complexes were formed at higher concentration. The azobenzene moiety was exploited for UV-light triggered dethreading of the complex. Between the PEG and β-CD a aromatic unit was incorporated that was competing in complexation with the azobenzene depending on the temperature, which was shown via temperature dependent NOESY.

A supramolecular enzyme polymer conjugate was described by Felici et al. [211]. β-CD functionalized PSty was prepared via ATRP that formed vesicles in aqueous

solution. These vesicles bear CD-units on the outer and inner surface. The β-CD moieties were subsequently utilized to conjugate adamantyl-PEG-functionalized horseradish peroxidase that showed catalytical activity although it was connected supramolecularly to the PSty vesicle.

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