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Polymerization of Included Monomers and Behaviour of Resulting Polymers

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Abstract Cyclodextrins (CDs) are of interest to synthetic chemists because of their chemical stability and the possibility to modify these molecules in a regioselective manner. For supramolecular chemistry CDs are of great importance, since they represent a homologous series of water-soluble and chiral host molecules which can be used as models for studying weak interactions. In addition, their low price provides motivation for the discovery of new applications. Thus, CDs are used for the solubilization and encapsulation of drugs, perfumes, and flavourings. These applications are due to their low toxicity and their biodegradablity. Finally, they are of general interest because they are obtained from a renewable resource, starch (Eggersdorfer, M., Warwel, S., Wulff, G.: Nachwachsende Rohstoffe Perspektiven für die Chemie. VCH, Weinheim (1993).

Keywords Cyclodextrin, Cyclodextrin complex, Hydrophilic hosts, Inclusion, Polymerization

Contents

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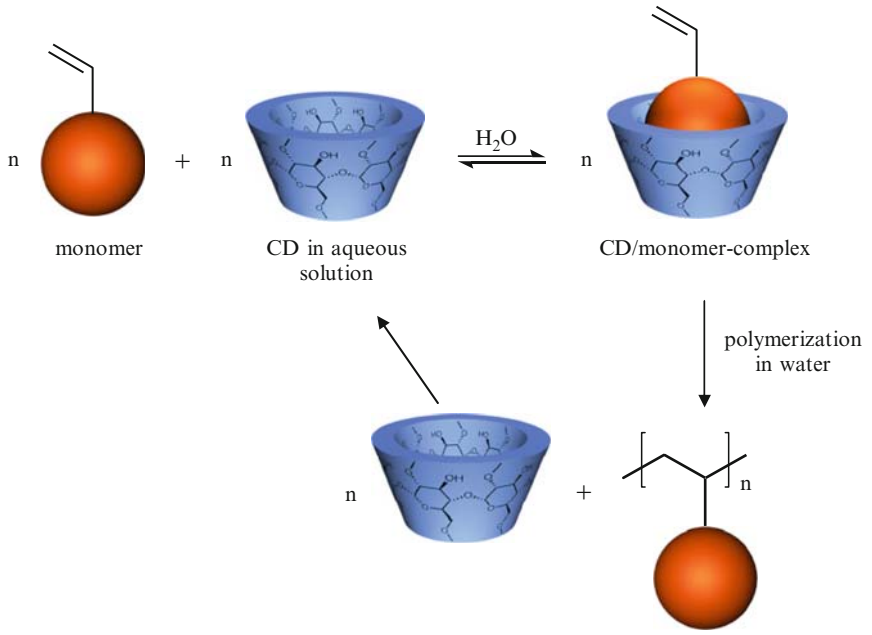
Abbreviations

AIBN	2,2′-Azobis(2-methylpropionitrile)
AMPS	2-Acrylamido-2-methylpropansulfonate
ANS	8-Anilino-1-naphthalinsulfonacid ammonium
CD	Cyclodextrin
2D-ROESY	Two-dimensional rotating-frame overhauser spectroscopy
DEF	Diethyl fumarate
DEM	Diethyl maleate
DMF	*N*,*N*-Dimethyl formaldehyde
DSC	Differential scanning calorimetry
MDAA	*N*,*N*-Dimethylacrylamide
EDT	3,4-Ethylenedioxythiophene
FT-IR	Fourier transformations infra red
GPC	Gel Permeation Chromatography
HPLC	High pressure liquid chromatography
LCST	Lower critical solution temperature
MALDI-TOF MS	Matrix assisted laser desorption ionization time of flight mass spectroscopy
Me	Methylated
M_w/M_n	Polydispersities
NIPAAM	*N*-Isopropylacrylamide
NMR	Nuclear magnetic resonance spectroscopy
r	Copolymerization parameters
RAFT	Reversible addition–fragmentation chain transfer
R_f	Retention factor
T_{crit}	Critical solution temperature
T_g	Glass transition temperature
t	Transparency
TLC	Thin layer chromatography
TTC	Thiocarbonylsulfanylpropionic acid
UV	Ultra violet spectroscopy
V50	2-Methylpropionamidine dihydrochloride
VA44	2,2′-Azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride

1 Cyclodextrins as Hydrophilic Hosts

A supramolecular structure results from defined non-covalent interactions between several individual molecules. [1–9]. Host–guest complexes [10–13] are important examples of this type of structure. The host molecule offers the guest molecule a suitable environment, generally a cavity (Scheme 1). The driving forces for complexation can arise from coulombic, dipole–dipole, van der Waals, hydrophobic, solvatophobic, or hydrogen bonding interactions between host and guest [14, 15]. The outer sphere of the host should be compatible with the required solvent in order to avoid aggregation or insolubility problems.



Scheme 1 Schematic illustration of complexation and polymerization of β-CD-complexed monomers

The formation of the complexes leads to significant changes of the solubility and reactivity of the guest molecules without any chemical modification. Thus, water insoluble molecules may become completely water soluble simply by mixing with an aqueous solution of native CD and CD derivatives, e.g. methylated (Me) or hydroxypropylated CD. The water solubility of these inclusion compounds enables detection of complex formation in solution by spectroscopic methods, such as NMR [16], UV, fluorescence, or circular dichroism spectroscopy, as well as by thermodynamic methods, e.g. microcalorimetry [17] or density [18, 19], or by solubility measurements. Likewise, mass spectrometry was used [20].

A crystal of the complexes suitable for X-ray diffraction analysis shows an orthorhombic structure, in which the guest molecule is complexed by the CD cavity (Fig. 1) [21, 22]. It is interesting to note that the complexes are packed in columns, and the CD toruses are tilted in an alternatively oriented way, wherein the orientation of the entire column can be either upwards or downwards. The guest molecules are located almost perpendicularly to the host.

2D–ROESY measurements can be evaluated along with the constitution of the complexes (Fig. 2) [23]. Cross peaks can be detected between the protons of the guest molecule and the inner protons of the Me-β-CD torus.

A further important and easy method to prove the formation of a complex is thin layer chromatography. For example, the R_f-values of methylated β-CD (Me-β-CD, $R_f = 0.69$) and uncomplexed phenyl methacrylate ($R_f = 0.92$) in methanol are significantly different from the values of the complex ($R_f = 0.54$) [24].

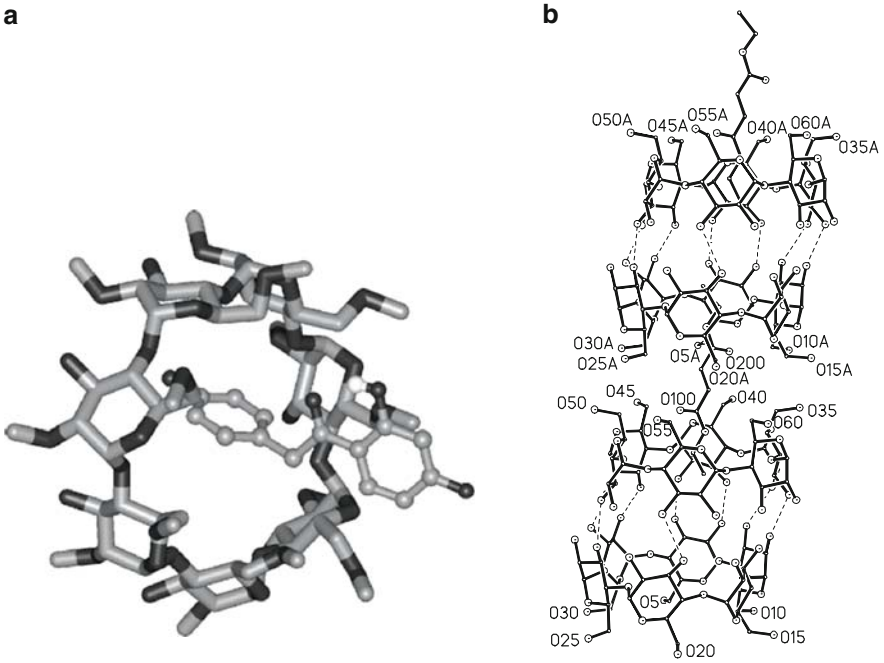


Fig. 1 **a** X-ray structure of 2,4-dihydroxyphenyl-4′-hydroxybenzylketone/Me-β-CD [21]. **b** Arrangement of α-CD dimers and diethyl fumarate molecules to columns along [001] in the crystal (note: packing of host/guest columns) [22]

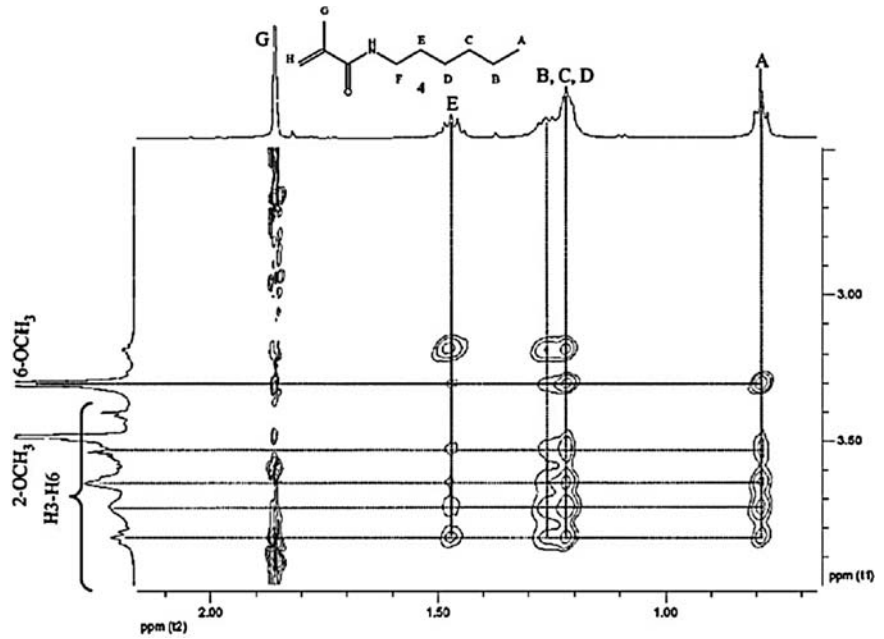


Fig. 2 2D-ROESY-NMR-spectrum of *N*-methacryloyl-1-aminohexane/Me-β-CD [23]

The FT–IR spectra of the complexed and uncomplexed guest molecules 11-(methacryloylamino)-undecanoic acid showed that the carbonyl bonds of the complexed monomer are shifted to higher frequencies from 1,708 to 1,712 cm^{-1}. This clearly indicates the influence of the host ring molecule on the carbonyl vibration [25].

2 Influences of CDs on Co- and Homopolymerization

We applied CDs to solubilize various types of vinyl monomers which are otherwise water insoluble. This unique behaviour of CD allows it to copolymerize hydrophobic monomers complexed in CDs with water soluble comonomers.

2.1 Polymerization of CD Complexed Monomers

In earlier works we reported on the preparation and structural analysis of 1:1 host–guest compounds of several types of CDs with pyrrole or 3,4-ethylenedioxythiophene (EDT), and their oxidative polymerization in water. These complexes were prepared simply by adding one equivalent of monomer to one equivalent of CD in water (Fig. 3) [26].

From some of these complexes, i.e. pyrrole/α-CD, EDT/α-CD, and EDT/β-CD, we were able to obtain single crystals that were studied by X-ray analysis. These show the herringbone fashioned cage-type crystal structure of pyrrole/α-CD, proving that it is a 1:1 complex with the pyrrole molecule located within the CD-cavity. The solid host–guest complexes are very stable under ambient conditions [21, 22]. After several weeks, the crystals remain unchanged while the unmodified monomers

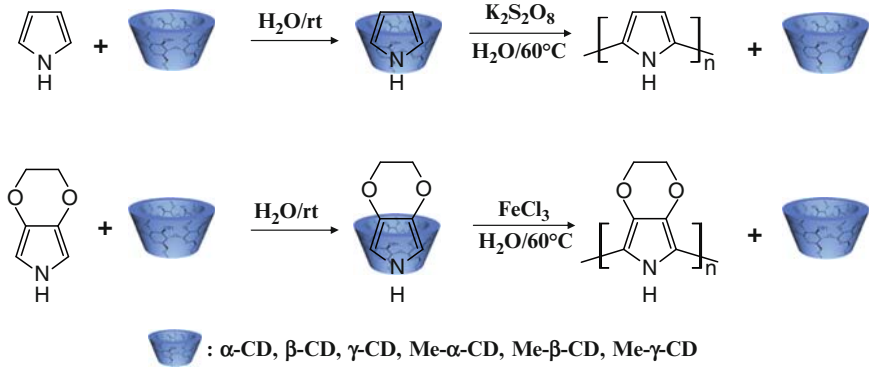


Fig. 3 Pyrrole or 3,4-ethylenedioxythiophene (EDT)/CD complex formation in water and oxidative polymerization of CD complexes

themselves change colour after a short time under the same conditions due to partial oxidation. Surprisingly, in the case of the EDT/α-CD, X-ray analysis showed the formation of a 1:1 non-inclusion channel-type packed supramolecular complex based on multiple hydrogen bonds. These colourless, crystalline pyrrole/CD and EDT/CD complexes that are barely soluble at room temperature were polymerized in water at 60°C under oxidative conditions.

All experiments showed that the corresponding polymers precipitated from solution. After filtration and washing with hot water, polypyrrole and poly(EDT) were obtained as dark powders in their oxidized state. Conductivity measurements showed that these materials have the same electrical properties $(10–100\,\mathrm{S\,cm^{-1}})$ as conventionally prepared polypyrrole or poly(EDT) [27, 28].

We also reported on the first examples of the free radical polymerization and copolymerization of a fluorinated 2-vinylcyclopropane monomer in aqueous solution via the host–guest complexation with Me-β-CD using a water-soluble initiator [29]. 2-Vinylcyclopropanes containing electron-withdrawing and radical-stabilizing groups are known to undergo radical ring-opening polymerization leading to polymers consisting predominantly, but not solely, of 1,5-linear olefin structures. The fluorinated vinylcyclopropane was homopolymerized in the presence of 7 mol equivalent of random Me-β-CD in aqueous medium at 60°C by the water-soluble azo initiator V50 within 2 h, in 50% yield (Fig. 4).

Fluorinated vinylcyclopropane was copolymerized with different ratios of hexyl substituted vinylcyclopropane via their respective complexes in Me-β-CD in

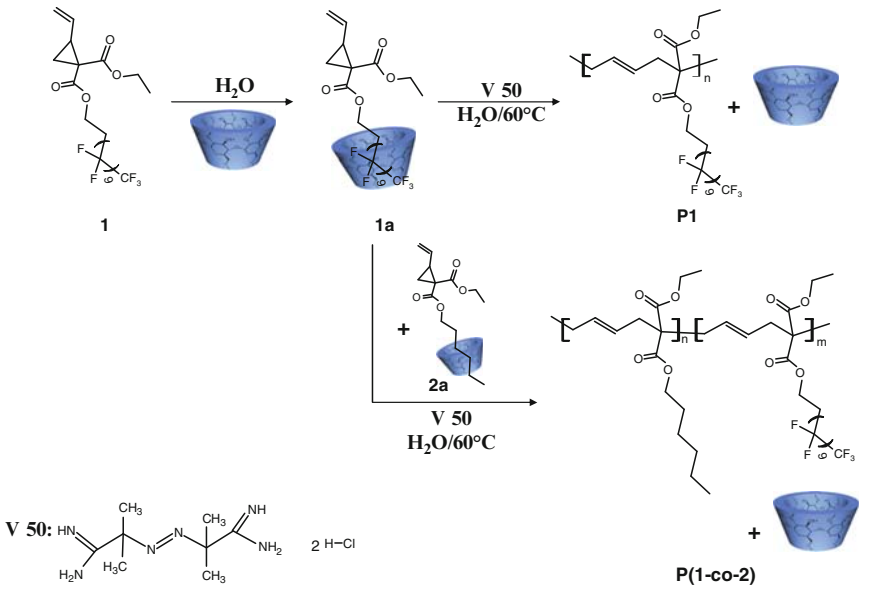


Fig. 4 Complexation of fluorinated vinylcyclopropane monomer with Me-β-CD and its homopolymerization and copolymerization with hexyl substituted vinylcyclopropane in aqueous solution

Table 1 Phase transition temperatures of fluorinated copolyvinylcyclopropanes (by DSC, scan rate 10°C min^{-1})

Polymer	**1** in copol. [mol%]	T_g [°C]	T_i[a] [°C]	ΔH_i[a] [J g^{-1}]
P(**1**-*co*-**2**)a	29	19	173	0.7
P(**1**-*co*-**2**)b	55	18	182	14.6
P(**1**-*co*-**2**)c	77	30	184	15.3
P**1**	100	35	188	14.1

[a]Smectic-isotropic or isotropization temperature and enthalpy

aqueous solution in an analogous manner (Table 1). The prepared polymers exhibited liquid crystal behaviour. No crystallinity was detected by our DSC analyses of the fluorinated copolymers and the thermotropic mesophases occurred above the glass transition temperature. The fluorinated homopolymer is known to form smectic phases [30], and we assume that consistently the copolymers poly(**1**-*co*-**2**) also formed a smectic mesophase. This was generated by the self-assembly of the fluorinated side groups into an ordered registry of smectic layers. The degree of order of the mesophase could vary with copolymer composition according to the different isotropization enthalpies measured.

It is noteworthy that the formation of a mesophase was sustained in the copolymers even incorporating low proportions of mesogenic fluorinated side groups. Moreover, the introduction of repeat co-units with hexyl substituents lowered T_g by internal plasticization and resulted in a somewhat broader mesophase range for the copolymers relative to the fluorinated homopoymer (e.g. $T_i - T_g = 164$°C for copolymer).

Furthermore, we have reported on the first examples of free radical homopolymerization and copolymerization of 2,3,4,5,6-pentafluorostyrene (**3**) with styrene (**5**) and its derivative 4-(*N*-adamantylamino)-2,3,5,6-tetrafluorostyrene (**4**) in aqueous solution via the host–guest complexation with Me-β-CD using water-soluble initiators (Fig. 5) [31]. The fluorinated monomers (**3** and **4**) and styrene (**5**) were complexed by Me-β-CD in water. The stoichiometries of the host-guest complexes were determined by NMR spectroscopy according to the Job method [32–34]. It was clearly shown that styrene (**5**) forms a defined 1:1 complex while the fluorinated monomers (**3** and **4**) are encapsulated by two Me-β-CD molecules. In the case of fluorinated monomer (**3**) this result was not expected since **3** and **5** have the same molecular scaffold and molecular modelling showed that the fluorinated styrene derivative **3** is only slightly bigger than styrene itself (Fig. 6) [35].

The Me-β-CD/monomer complexes **3a** and **4a** were homopolymerized in water at room temperature using the redox initiator system $K_2S_2O_8/Na_2S_2O_5$ (Figs. 6 and 7). To compare our technique with traditional polymerization methods, all polymerizations were also carried out starting from the free monomers **3**, **4**, and **5** in organic solvents (toluene or benzene) at 80°C using AIBN as initiator (Table 2).

In all cases almost quantitative yields of the homo and copolymers from complexed monomers were obtained. Poly(pentafluorostyrene) (**P3a**) and polymer

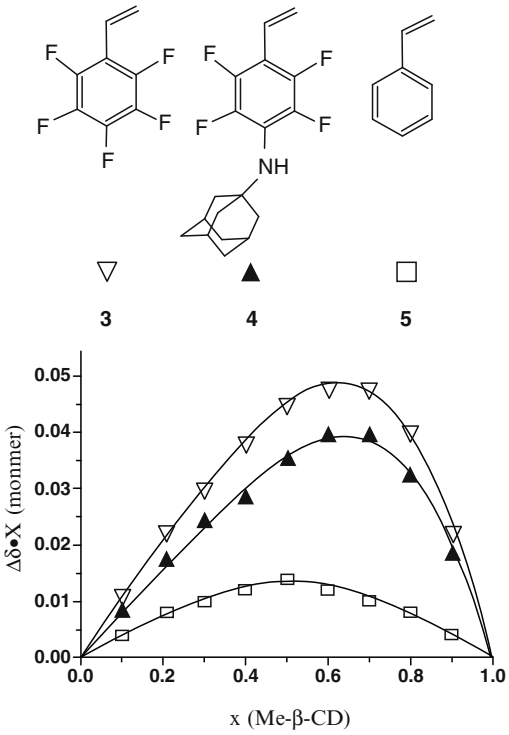


Fig. 5 Job plots by considering the shifts of protons of three kinds of monomers in the presence of Me-β-CD

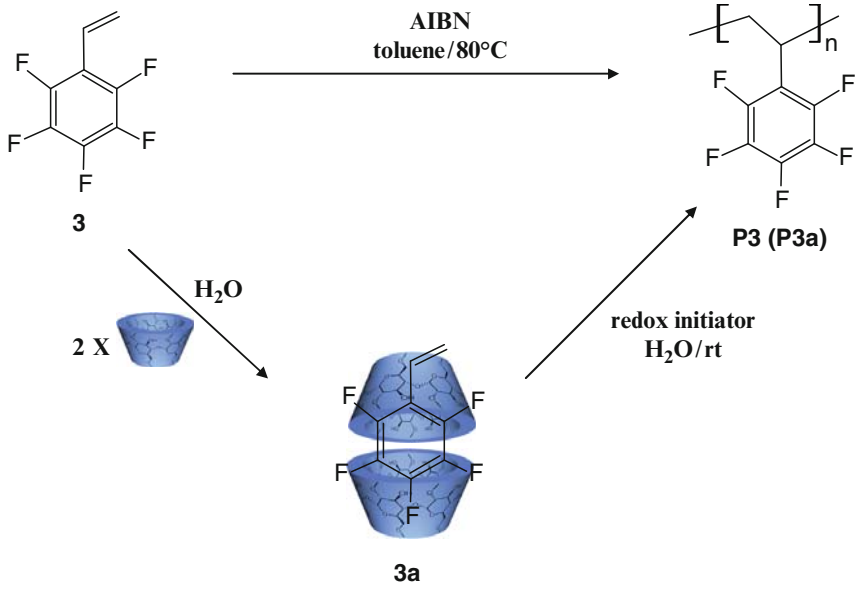


Fig. 6 Homopolymerization of pentafluorostyrene in toluene and water by CD-complexation of the monomer respectively

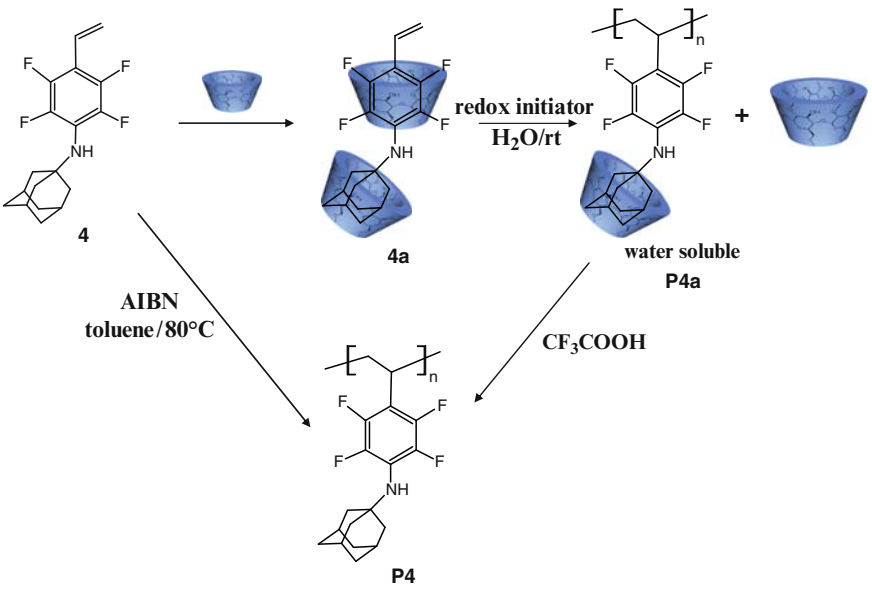


Fig. 7 Homopolymerization of free monomer in toluene and with Me-β-CD in water followed by degradation of Me-β-CD with trifluoroacetic acid

Table 2 Characterization of obtained polymers

Polymer	Monomer	Solvent	T [°C]	M_n	PD	T_g
P3a	**3a**	CD/water[a]	25	5,600	2.1	100
P3	**3**	Toluene[b]	80	4,500	1.5	90
P4a	**4a**	CD/water[a]	25	11,900	3.2	
P4	**4**	Toluene[b]	80	12,300	3.1	
P(3a-*co*-4a)	**3a,4a**	CD/water[a]	25	11,400	3.0	103
P(3-*co*-4)	**3,4**	Toluene[b]	80	4,500	1.5	90
P3-1	**3**	CD/water[a]	80	10,900	2.0	104
P3-2	**3**	Water[c]	80	38,500	3.2	106

[a]Redox initiator

[b]AIBN

[c]$K_2S_2O_8$, semibatch polymerization

P(3a-*co*-4a) could be isolated via simple filtration (Table 2). Polymer **P4a** was completely water-soluble due to the presence of non-covalently attached Me-β-CD. After treatment with trifluoroacetic acid to decompose the Me-β-CD ring, polymer **P4** precipitated after some hours and could be isolated by filtration (Fig. 7).

As an example, myrcene, an isoprene dimer, is found in many natural oils. Most of the polymerizations of myrcene were affected by a metal catalyst in organic solvents [36–39]. We tried to synthesize copolymers containing myrcene, styrene and diethyl fumarate (DEF) by using Me-β-CD in water (Fig. 8) [40].

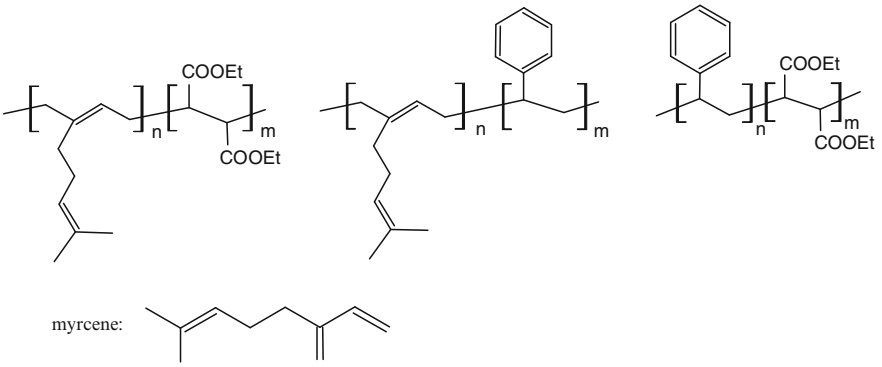


Fig. 8 Copolymers containing myrcene, styrene and diethyl fumarate (DEF) after Me-β-CD mediated copolymerization using redox initiator in aqueous media

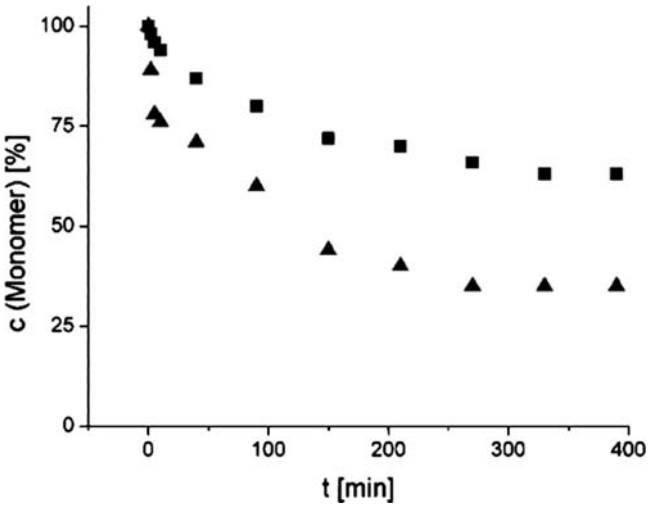


Fig. 9 Kinetic plots of the radical copolymerization of a 1:1 molar mixture of CD-complexed styrene (*filled triangles*) and diethyl fumarate (*filled squares*) in water at room temperature (using 2.5 mol% redox initiator $K_2S_2O_8/Na_2S_2O_5$)

We have found that the polymerization in homogenous, aqueous CD solution is normally much faster and ends up with higher yields and molecular weights than polymerization under similar conditions in an organic solvent [41,42]. The polydispersities (M_w/M_n) of polymers were similar in all cases. Only the M_w/M_n values of the polymer containing styrene monomer units showed higher values.

The copolymerization of CD-complexed styrene and DEF led to a precipitation of the corresponding water-insoluble copolymers [43]. The reactivity of the styrene complex is higher than that of complexed DEF. The conversions of both monomers were finished after about 6 h at room temperature. The lower reactivity of DEF in comparison to styrene can be explained by the fact that the double bond is sterically hindered by the two ester groups in the *trans*-1,2 position (Fig. 9).

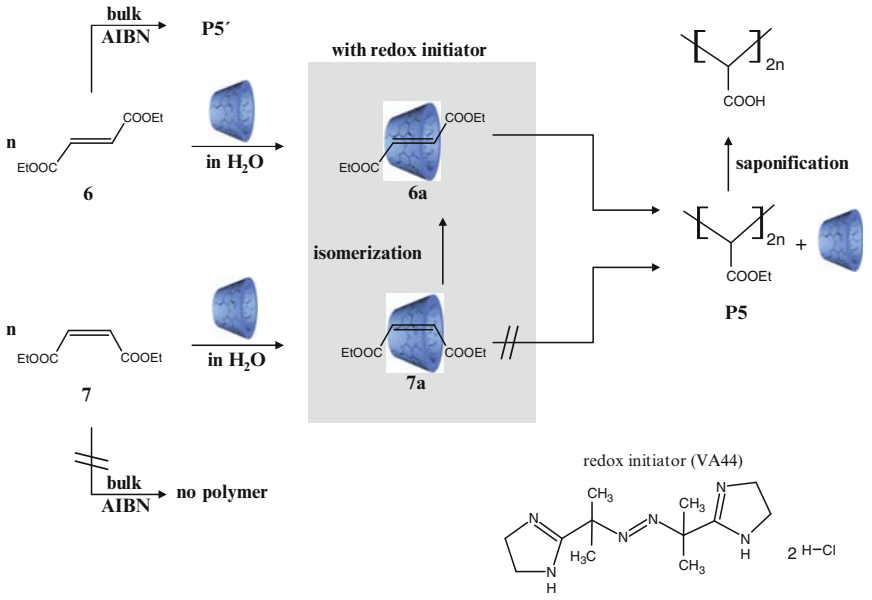


Fig. 10 Preparation of poly(ethoxycarbonylmethylene) from **6** and **7** with/without Me β-CD

Additionally, the double bond is preferentially covered by the CD ring. In contrast, the double bond of styrene is located more or less out of the CD centre, which allows easy access of the growing radicals. Furthermore, copolymerization parameters indicate that styrene is incorporated preferentially into the copolymer chain ($r_{\text{styrene}} = 1.95 \pm 0.02$ and $r_{\text{DEF}} = 0.97 \pm 0.01$). The reduced rate of copolymerization of DEF with styrene-rich compositions remains constant up to a fairly high conversion. It can be shown from the r_{styrene} and r_{DEF} values that the monomer composition changes during the progress of the reaction. Thus, the consumption of the DEF monomer is slower than that of styrene, leading to polymer compositions with an increased amount of homo segments. The strong influence of CD on the copolymerization parameters becomes obvious when comparing the values given in the literature for polymerization in an organic solvent ($r_{\text{styrene}} = 0.36 \pm 0.04$ and $r_{\text{DEF}} = 0.10 \pm 0.02$) giving rise to almost alternating copolymers [44]. In contrast to this, the CD-complexed monomers copolymerize in a completely different manner, as discussed above.

DEF (**6**) and diethyl maleate (DEM, **7**) were complexed with equimolar amount of Me-β-CD and polymerized with redox initiator ($K_2S_2O_8/Na_2S_2O_5$) at room temperature and with VA44 at 50°C in aqueous media (Fig. 10) [22]. The homopolymerization of CD complexed monomers **6a** and **7a** with redox initiator led to a precipitation of the corresponding water-insoluble polymer **P6**, which was separated by centrifugation.

Normally, the maleic ester *cis*-isomers do to not give any homopolymer under similar condition as applied in the case of *trans*-isomers [45–47]. Surprisingly, in

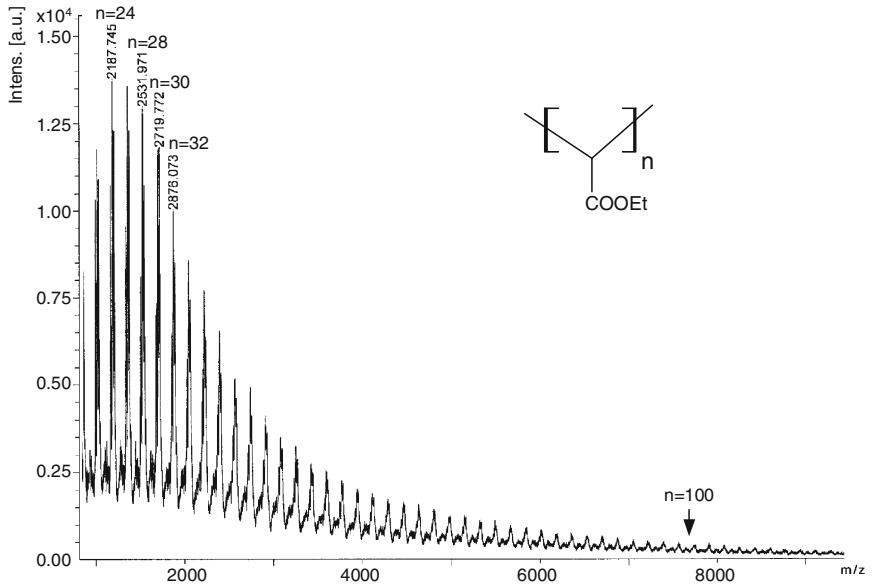


Fig. 11 MALDI-TOF spectrum of polymer **P5**

the presence of both Me-β-CD and redox initiator **7** undergoes homopolymerization via complexation with CD to give poly(ethoxycarbonylmethylene) **P5**. We evaluated the independent potential influence of CD and redox initiator on observed isomerization. It was shown that in the presence of only one of the components no isomerization takes place. Since **7** can be radically polymerized via a *cis-trans*-isomerization of the monomer, this reaction obviously needs both redox initiator and CD (Fig. 10).

The molecular weight of polymer was estimated by MALD-TOF MS (Fig. 11). The peaks show exactly the molecular masses of the polymers. The glass transition temperature (T_g) of the polymers obtained from DEF **6** and DEM **7** are almost identical. The effective CD-mediated homopolymerization reactivity of **6a** and **7a** are visualized in Fig. 12. The uncomplexed monomers **6** and **7** did not polymerize under the same conditions.

The unreacted residual *trans*-monomer was found to consist of only fumarate after polymerization of the complex **6a** by means of HPLC. In contrast, the residual **7a** was detected to consist of *cis*- and *trans*-isomer during the polymerization. This means that the complexed *cis*-isomer **7a** isomerized to *trans* configuration in the presence of radicals. Figure 13 shows the chromatograms of monomers obtained during the polymerization of complex **7a** with redox initiator. It indicates that the peak of *trans*-monomer increased with increasing reaction time. Therefore, it was clear that the polymerization of *cis*-olefin monomers **7** in the presence of both CD and redox initiator takes place via an isomerization radical polymerization

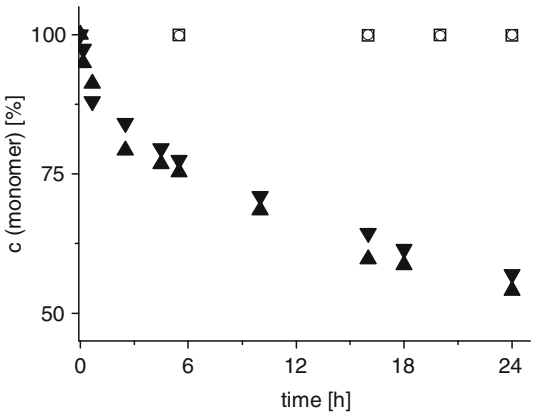


Fig. 12 Kinetic plot of homopolymerization of methylated β-CD-complexed monomer **6a** (*filled triangles*) and **7a** (*filled inverted triangles*) and CD-uncomplexed monomer **6** (*open squares*) and **7** (*open circles*) using redox initiator in aqueous media at room temperature

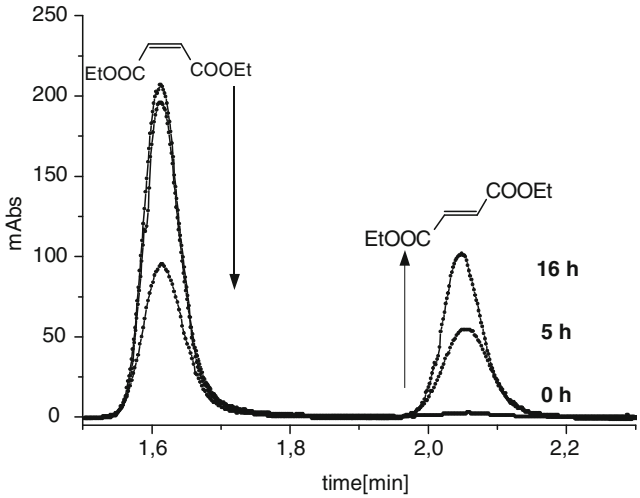
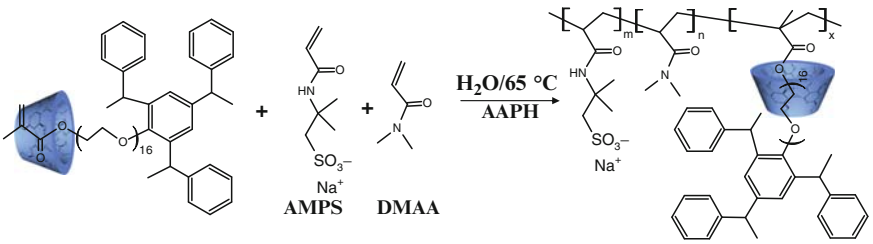


Fig. 13 HPLC Chromatograms of **7a** showing *cis/trans* isomerization during the polymerization with redox initiator ($R_{f(DEM)} = 1.63$ and $R_{f(DEF)} = 2.50$)

mechanism, i.e. maleates radicals isomerize first into fumarates and then these fumarates undergo radical polymerization.

Copolymerization of the CD-complexed macromonomer **8a** with hydrophilic comonomers 2-acrylamido-2-methylpropansulfonate (AMPS) and *N*,*N*-dimethylacrylamide (DMAA) leads to formation of hydrophobically associative polymers (Fig. 14) [48].

To study the aggregation of the synthesized polymers, 8-anilino-1-naphthalinsulfonacid ammonium (ANS) was used as the fluorescence probe. ANS has a minimum solubility of $28\,g\,L^{-1}$ in water but a higher solubility in hydrophobic media. With increasing polarity of the media its fluorescence intensity increases sensitively, and a simultaneous blue shift of the fluorescence band was also



	m:n [mol]	content of 8 [wt.%]
P6	4.1:1	1.0
P7	4.1:1	3.0
P8	3.8:1	4.9

Fig. 14 Synthesis of hydrophobically associative polymers **P6, P7** and **P8**

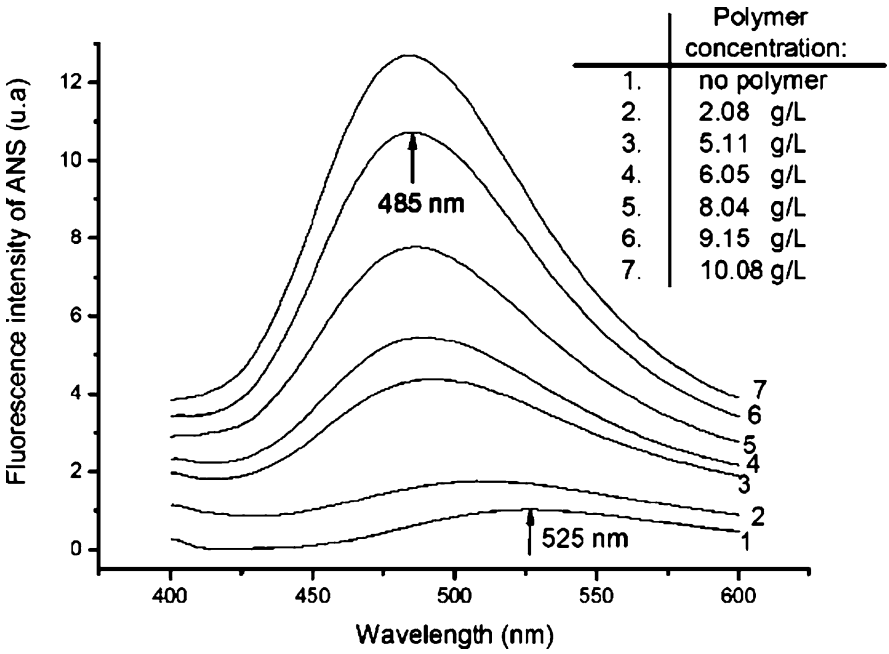


Fig. 15 Fluorescence spectra of ANS in differently concentrated aqueous solution of polymers at RT (**P8**:contains 5 wt% of the macromonomer)

observed. Its fluorescence is independent on pH value for pH $>$ 6. Therefore, ANS is a suitable fluorescence probe to study the aggregation of the polymers (**P6**–**P8**) [49]. According to Fig. 15 the fluorescence spectra of ANS in differently concentrated aqueous solutions of polymer **P8** indicate the potential aggregation. It is interesting to note that the copolymer is a sidechain polyrotaxane. The content of CD was proved by GPC equipped with a chiral detector.

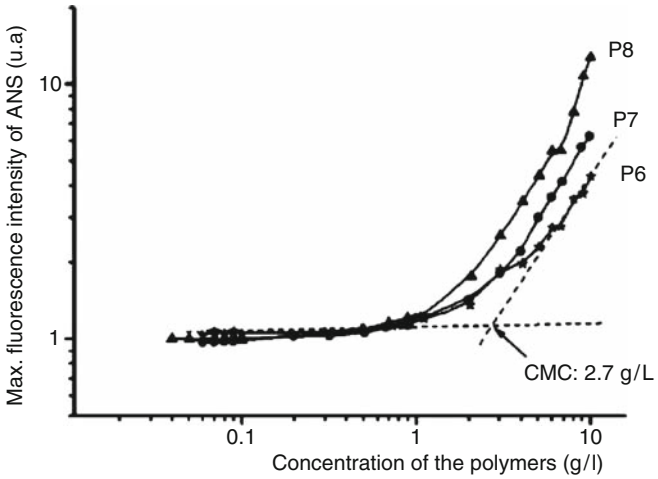


Fig. 16 Plots of the maximum fluorescence intensity as a function of polymer concentration at RT (**P6**: 1.0 wt% of 8; **P7**: 3.0 wt% of 8; **P8**: 4.9 wt% of 8)

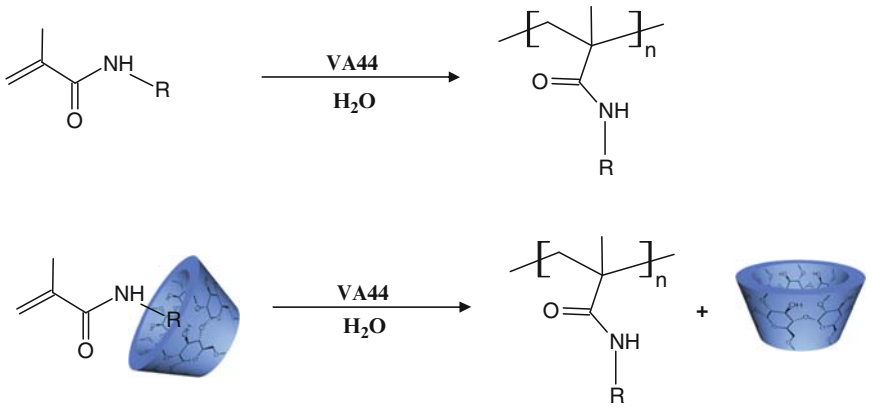
In Fig. 16 the maximum fluorescence intensity of ANS was plotted against the concentration of the polymers with different content of associative macromonomer (**P6**–**P8**). In diluted polymer solutions, the maximum fluorescence intensity increased gradually with increasing polymer concentration. At the same polymer concentration, ANS showed higher fluorescence intensity in a solution of polymer that contains more of the associative macromonomer **8**.

The monomers *N*-methacryloyl-1-aminopropane (**9**), *N*-methacryloyl-1-aminobutane (**10**), *N*-methacryl-oyl-1-aminopentane (**11**), and *N*-methacryloyl-1-aminohexane (**12**) are synthesized directly from the corresponding amine and methacrylic acid by microwave irradiation [50], or classically by the treatment of amines with methacryloyl chloride (Fig. 17).

^{1}H–NMR spectroscopic measurements were carried out to investigate the stoichiometry of the CD complexes [51]. D_2O is used as the solvent at pH 7.3 and different mole fractions are considered ranging from 0.1 to 1.0 at increments of 0.1 with Me-β -CD as the host. The plot of $-\Delta\delta^* \bullet X_{CD}$ vs the mole fraction X_4 for the Me-β -CD-complexed hexyl methacrylamide (**12a**) shows a maximum at $X_4 = 0.50$. This is a strong hint that a 1:1 complex was formed (Fig. 18).

The hydrodynamic volumes of both Me-β-CD and the Me-β-CD complexes were measured by use of dynamic light scattering to prove the existence of molecularly dispersed complexes. Interestingly, results indicate that no aggregates are formed. However, because of guest monomer incorporation the hydrodynamic volume of the complex increases slightly in comparison to Me-β-CD (Fig. 19).

To evaluate the effect of Me-β-CD on polymerization kinetics, the free uncomplexed monomers **9**–**12** and the corresponding Me-β-CD complexes (**9a**–**12a**) are homopolymerized in water by a free radical mechanism under identical conditions. In the case of the aqueous polymerization of the free monomers **9**–**12** the initial



monomer	R	polymer
9/9a	n-propyl	P9/P9a
10/10a	n-butyl	P10/P10a
11/11a	n-pentyl	P11/P11a
12/12a	n-hexyl	P12/P12a

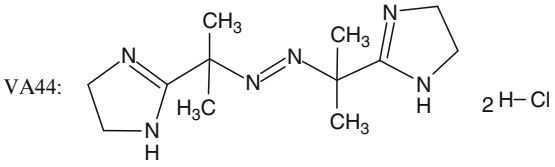


Fig. 17 Structures of the complexed Me-β-CD monomers and subsequent polymerization

polymerization rate increases with increasing water solubility. The opposite effect is observed in the case of the polymerization of the Me-β-CD complexed methacrylamide monomers **9a**–**12a**. The polymerization rates are increased with increasing alkyl chain length of the complexed monomers **9a**–**12a** and the decreasing water solubility of the free monomers **9**–**12** (Fig. 20).

2.2 Polymerization of a CD Complexed Photoinitiator and a Water Soluble Monomer

For evaluating the influence of CD on the photoinitiated polymerization process, the polymerization of a water soluble monomer, *N*-isopropylacrylamide (NIPAAM), using complex of Me-β-CD and 2-hydroxy-2-methyl-1-phenylpropan-1-one (**13**) as

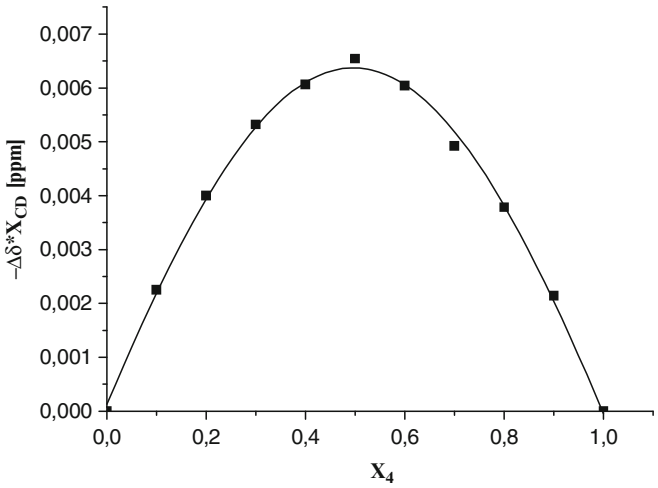


Fig. 18 Job plot of the complex of monomer **12a** in D_2O with Me-β-CD (pH 7.3), the maximum is at $X_4 = 0.50$

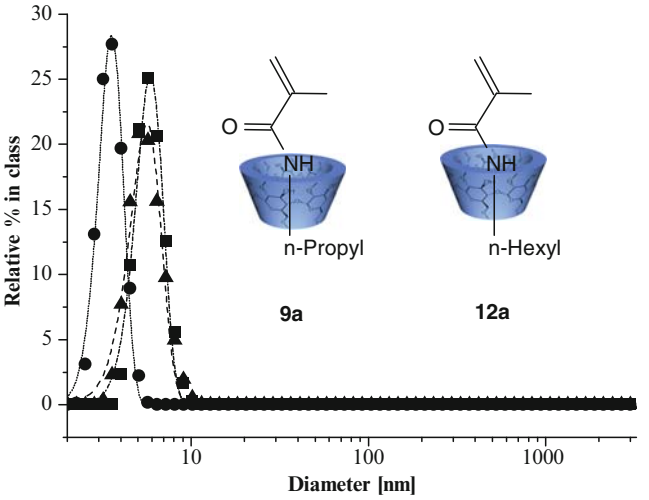


Fig. 19 Particle size distribution by dynamic light scattering of free Me-β-CD (*filled circles*) and Me-β-CD complexes **9a** (*filled squares*) and **12a** (*filled triangles*) in water at 50°C

the initiator, was performed in aqueous medium [52]. After the addition of 2 mol% of photoinitiator or CD-complexed photoinitiator the mixtures were irradiated simultaneously at constant temperature (20°C) with a high-pressure mercury lamp as the light source. In accordance with TLC measurements the photo initiator stays in the complexed form also in the presence of NIPAAM monomer, indicating that the equilibrium between free monomer and CD-monomer complex can be neglected.

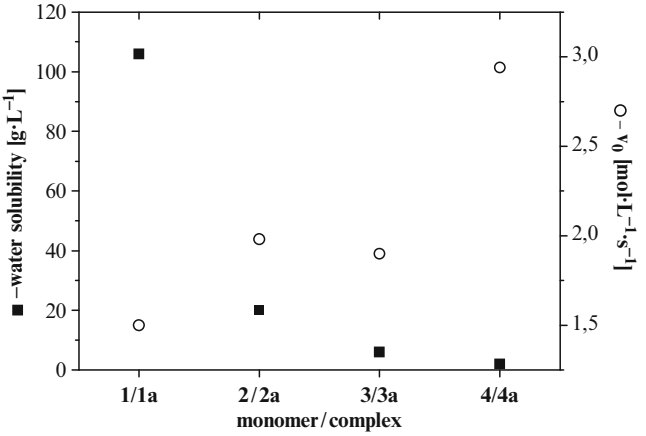


Fig. 20 Initial polymerization rate v_0 of CD complexed monomers **9a–12a** (*open circles*) vs water solubilities of monomers **9–12** (*filled squares*)

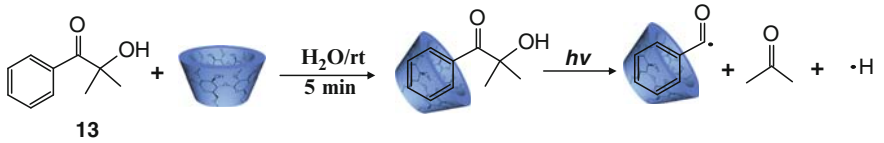


Fig. 21 Preparation of the CD-photoinitiator complex in water and proposed decomposition mechanism of the complex

UV spectroscopic measurements revealed that the polymerization reaction initiated with CD-complexed photo initiator is faster and, thus, ends up with higher yields than the polymerization reaction initiated with the same molar concentration of uncomplexed photo initiator. Radical photo polymerization is achieved by the homolytic fragmentation of carbon–carbon bonds of a photo-excited molecule as illustrated in Fig. 21.

2.3 Polymerization of CD Complexed Monomer and Water Soluble Monomer

Copolymerization of CD complexed myrcene (**14**) and NIPAAM was carried out (Fig. 22). The obtained polymer **P13** was water soluble and little amounts of CD still remained in the polymers as detected by ^{1}H NMR spectroscopy. The thermosensitive properties of aqueous solutions of copolymers were investigated by monitoring the changes of turbidity as a function of temperature. Surprisingly, **P13** shows exceptional high LCST transition temperature of 80°C. Thus, the turbidity points of copolymers is significantly higher than of poly(NIPAAM) itself (32°C) because of the existence of hydrophilic CD complexes of the side groups.

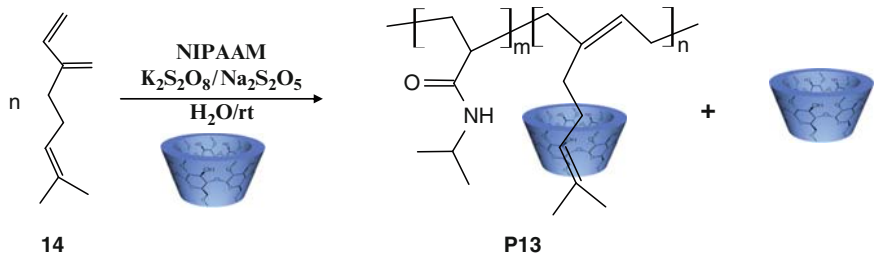


Fig. 22 Polymerization of CD-complexed myrcene with NIPAAM in H_2O using redox initiator

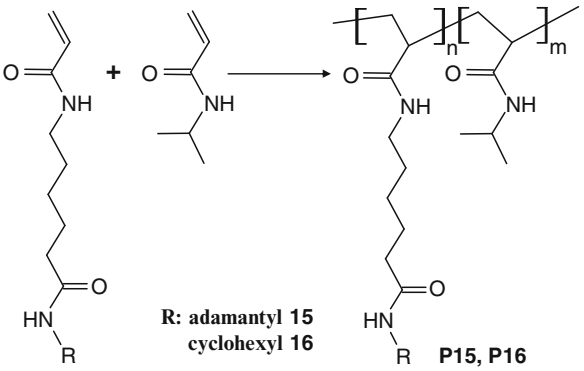


Fig. 23 Radical copolymerization of acrylamide with R = adamantyl (**15**) or cyclohexyl (**16**) and NIPAAM in DMF without any host compound; n/m = 1 : 20

The LCST value can be influenced, for example, by copolymerization of NIPAAM or by chemical modification of the acrylamide polymer itself. The slightly cross-linked LCST polymers, so-called hydrogels, find potential application in the medical and biochemical fields, for controlled drug delivery [53] and as materials for bioreactors [54]. One general explanation of the LCST effect is that strong hydrogen bonds exist between water molecules and the hydrophilic groups of the polymer at low temperature [55]. With increasing temperature, intramolecular interactions between hydrophobic chain components of the polymer increase.

For the investigation of the LCST behaviour further NIPAAM containing copolymers containing hydrophobic adamantine or cyclohexayl groups were synthesized (Fig. 23) [56–59].

Optical turbidity measurements showed a LCST for aqueous solutions of **P14** up to 17°C. On the other hand, solutions of copolymer with cyclohexyl **P15** have a transition at 31°C, which is 4°C lower than that of pure NIPAAM polymer **P16** (Table 3). The lower LCST for **P15** compared to **P16** is attributed to the hydrophobic effect [60], which is the decrease of the LCST with increasing numbers of hydrophobic side-chain groups.

In addition, the thermosensitive properties of aqueous solutions of copolymers **P17–P19** and of their supramolecular non-covalent cross-linked networks were

Table 3 The properties of the synthesized copolymers

Polymer	LCST [°C]	n/m	M_n [g mol^{-1}]	PD
P14	17	1:20	17,400	2.90
P15	31	1:20	16,100	3.58
P16	35	–	71,000	6.18

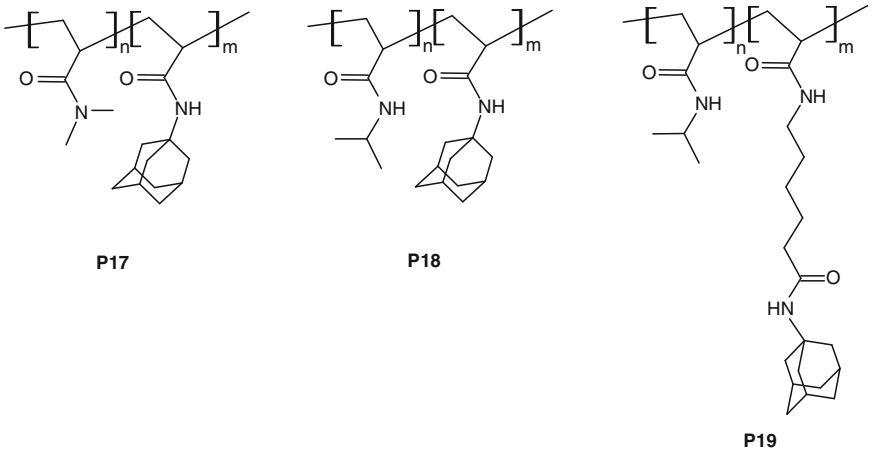


Fig. 24 NIPAAM and *N*,*N*-dimethylacrylamide containing copolymers (n : m = 20 : 1)

investigated by monitoring the changes of turbidity as a function of temperature [61,62]. The *N*,*N*-dimethylacrylamide-containing copolymer **P17** shows no turbidity point at temperatures between 10°C and 90°C in water. For copolymer **P18** we obtained the LCST transition at 23°C; for copolymer **P19** we found a cloud point of 21°C (Fig. 24). Both copolymers showed a sharp phase transition in response to a small temperature change. The fact that the turbidity points of copolymers **P18** and **P19** are significantly lower than that of poly(NIPAAM) itself (32°C) is caused by the hydrophobic adamantyl units in the copolymers; copolymers **P18** and **P19** are less soluble in water than a homopolymer of NIPAAM.

To investigate the effect of adding monomeric and dimeric CD on the change of phase transition temperature of the polymers **P18** and **P19**, we performed turbidity measurements at the same polymer concentration as above in the presence of a defined amount of Me-β-CD and CD dimer, respectively (Fig. **25 a,**b) [61,62]. As reported previously [56–59], we found that addition of Me-β-CD led to cloud points of polymers **P18** and **P19** of 32°C, which correlates to the LCST of pure poly(NIPAAM). This increase of the cloud points relative to the cloud points of pure **P18** and **P19** results from the inclusion of the hydrophobic adamantyl units by Me-β-CD.

When a CD dimer was added to the aqueous polymer solutions at half the molar ratio (relative to the amount of Me-β-CD), the cloud points decreased significantly. This observed effect again can be explained by the supramolecular

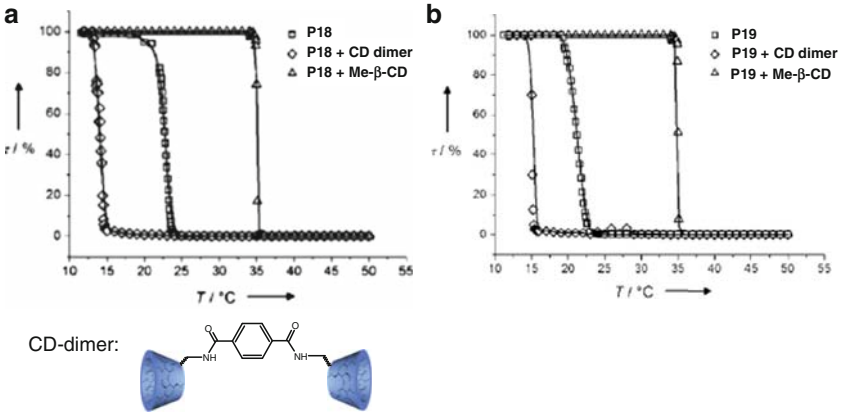


Fig. 25 a,b Turbidity measurements of aqueous solutions of the polymers **P18 a** and **P19 b** without addition of host molecules and measurements of the supramolecular complexes of the polymers with CD dimer and Me-β-CD respectively. $C_P = 10\,g\,L^{-1}$, $C_{Me\text{-}\beta\text{-}CD} = 10\,g\,L^{-1}$, and $C_{CD\ dimer} = 5\,g\,L^{-1}$, 10°C

cross-linkage of single polymer chains upon complexation of the CD dimer. The resulting supramolecular structures are restricted in their mobility and solubility, which is reflected in cloud points of 14.0°C for polymer **P18** and 15.7°C for polymer **P19**. As a result of the LCST behaviour of the polymer/CD dimer mixtures the obtained hydrogels show different transparencies. The gel formed from copolymer **P17** is transparent at room temperature, whereas those from polymers **P18** and **P19** are turbid at room temperature and transparent below their cloud points of 14.0°C and 15.7°C, respectively.

As another example, when the transparent solutions of the complexed polymers **P20a** were heated above 70°C, a sudden turbidity was observed [63, 64]. Surprisingly, when the solution was cooled, transparency was completely restored. Exact turbidity measurements were performed to evaluate the solubility as a function of temperature. We found that the complexed monomer **17a** is completely soluble in the temperature range 10–85°C. This means that the monomer complex is stable enough to keep the monomer in solution independent of temperature. In contrast, the polymer complex **P20a** showed a definite clouding point at a temperature of 54°C for the heating run (Fig. **27 a,**ba) and a clearing point of about 50°C for the cooling run (Fig. **27 a,**bb).

These temperatures were found to be a function of the molecular mass of the β-CD-free polymers. Figure 26 shows the reversible decomplexation–complexation process of polymer **P20** in water. The transmittance change of a solution of **P20a** is plotted as a function of temperature in Fig. **27 a,**b. The decrease in the transmittance of the complexed polymer to 0% occurs within a temperature interval of roughly 5°C. In the subsequent cooling step the polymer returns to solution by new formation of polymer/β-CD complex. In contrast, the β-CD free polymer is not soluble in water at any temperature in this range.

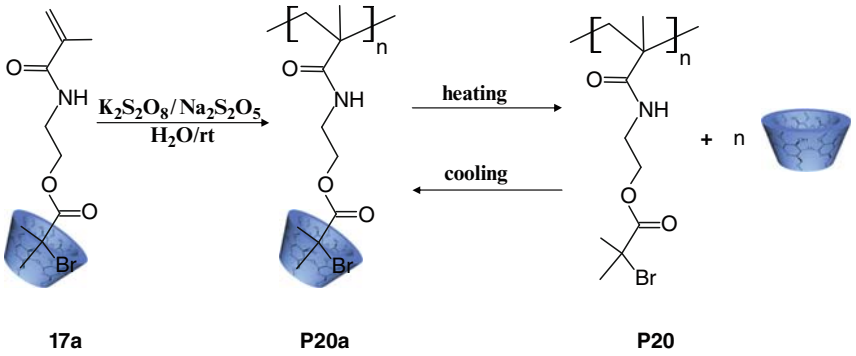


Fig. 26 Temperature-dependent reversible unthreading of CD from the bulky side group of **P20a** during the heating procedure

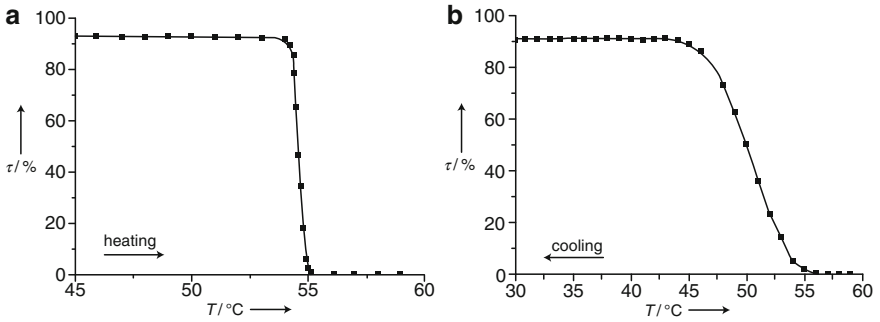


Fig. 27 a,b Transmittance of a solution of complexed polymer **P20a** vs temperature during heating **a** and cooling **b**

The interesting polymer-solubility behaviour led us to compare this phenomenon with classical LCST effects. In our case, because of the reversible complex formation between the polymer **P20** and CD, the optical effect is based on supramolecular interactions. This means that the discovered pseudo-LCST behaviour is a result of non-covalent interactions between the CD host and polymer guest. Furthermore, in this system competitive inhibition or control of the LCST is possible by addition of other suitable guest molecules of low molecular weight, for example, potassium 1-adamantylcarboxylate. CD complexes these molecules preferably and the polymer precipitates. This special effect cannot be observed in regular LCST systems.

A further important application of CD is the preparation of relatively low polydispersity polystyrenes (compared to radical CD polymerization) using the water-soluble RAFT reagent 3-benzylsulfanyl thiocarbonylsulfanylpropionic acid (TTC) complexed in aqueous Me-β-CD solution (Fig. 28) [65]. This method also allows the direct synthesis of amphiphilic block copolymers in aqueous solution without compatibility issues.

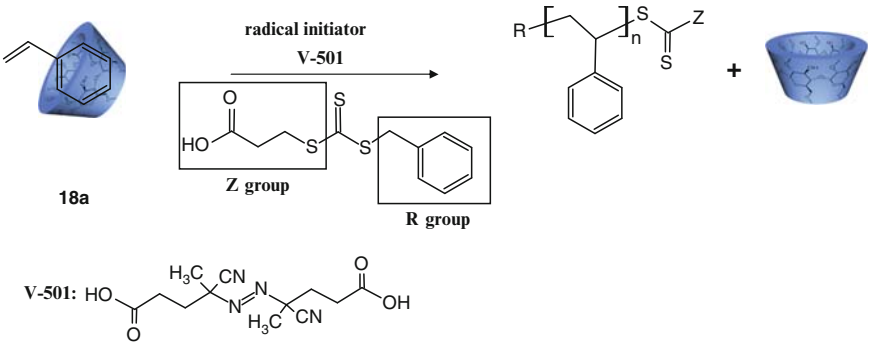


Fig. 28 Schematic presentation of complexation and RAFT polymerization of Me-β-CD complexed styrene **18a** with 3-benzylsulfanylthiocarbonylsulfanylpropionic acid (TTC) as RAFT agent

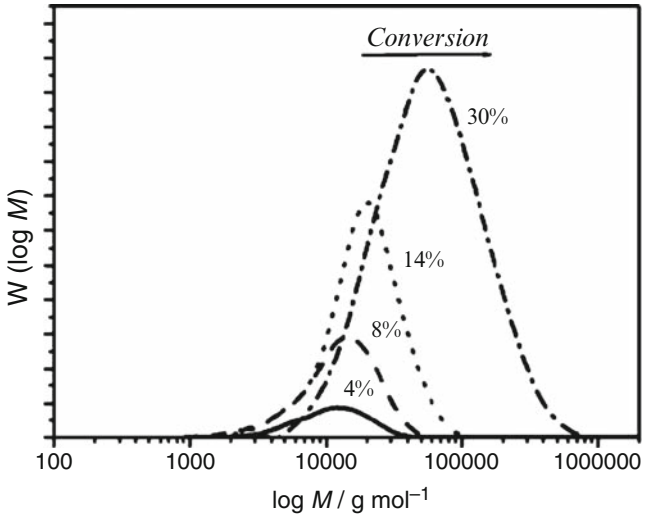


Fig. 29 Evolution of the full molecular weight distributions in the CD-mediated styrene RAFT polymerization in aqueous solution at 70°C. RAFT agent/initiator to 10:1. Samples were taken after 75, 180, 300 and 420 min, respectively. The individual conversions to polystyrene are given within the figure

Controlled living radical polymerization of CD-complexed styrene in water can be conducted via the RAFT process, especially at low conversion (<20%). The molecular weight of PS can be controlled by variation of the RAFT agent concentration and the number-average molecular weight increases linearly with conversion (Fig. 29).

The polymers produced with the CD-RAFT system exhibited narrower polydispersities ($1.23 < M_w/M_n < 2.36$) than those without RAFT agent ($5.24 < M_w/M_n < 9.21$). However, the polydispersities in the CD-RAFT system are considerably higher (especially at increased conversions) than those in conventional (bulk or

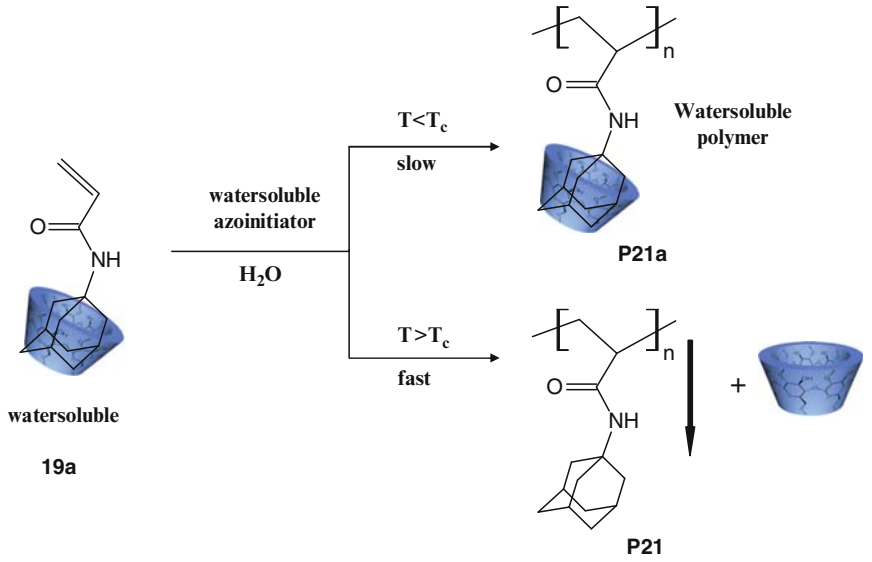


Fig. 30 Schematic illustration of the polymerization of **19a** using 1 mol% water-soluble azo initiator (VA044) at different temperatures in water

solution) RAFT systems and the molecular weight evolution deviates considerably from the theoretically expected one. We attribute these effects to the continuous precipitation of the polymer with increasing conversion, which effectively leads to a hybrid system between conventional and controlled living free radical polymerization.

Furthermore, we investigated temperature-dependent solution behaviour of Me-β-CD with poly(meth)acrylamides bearing bulky hydrophobic side groups (Fig. 30) [66].

The free radical polymerization of complexed monomer **19a** was carried out at different temperatures in water in the presence of 1 mol% water-soluble azoinitiator. The temperature range of interest was 50–90°C, to determine v_0 below and above the T_{crit} of 65°C of the given CD-polymer system (**P21a**).

In Fig. 31, the transparency τ of an aqueous solution of **P21a** is plotted against the temperature. While heating, it can be observed that the transparency of the solution of **P21a** decreases from almost 100% to 0% around 65°C (±3°C). We would like to emphasize that the point of turbidity certainly depends on the sample concentration. With increasing concentration of CD, the LCST shifts to higher values [67,68]. During the cooling phase, the water insoluble polymer **P21** remains insoluble. However, the reformation of the complex **P21a** takes place within 12 h of stirring at room temperature or below. We suspect that, once precipitated, the bulky adamantyl-side group of polymer **P21** is hardly accessible by the Me-β-CD, so that reconstitution of the complex **P21a** takes hours (Figs. 30 and 31).

The complexation–decomplexation equilibrium of the polymer is strongly entropy driven. The monomer complex **19a** (Fig. 30) is stable up to 100°C, since it

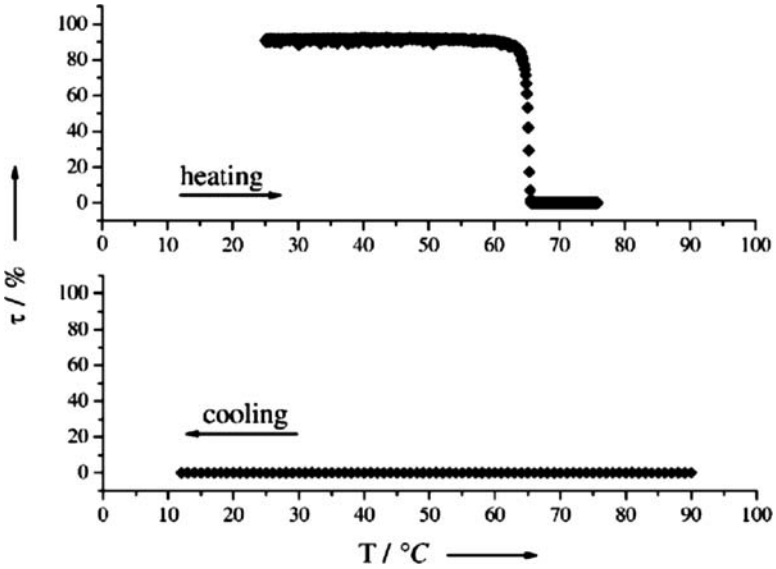


Fig. 31 Transparency t of an aqueous solution of **P21a** ($c = 30\,\mathrm{g\,L^{-1}}$) against the temperature during heating and cooling

has a high mobility in solution. However, in contrast, a strong increase in total mobility of the polymer system takes place above T_{crit} because the CD rings are released from the polymer.

The incorporation of a flexible spacer between the polymer backbone and the adamantyl groups strongly affects the thermosensitive properties of the supramolecular complex [67,68]. In Fig. 32, the turbidity measurement of a $100\,\mathrm{g\,L^{-1}}$ aqueous solution of polymer/Me-β-CD-complex **P22a** is presented. The heating run indicates the cloud point of **P22a** at 38.6°C, which is 6°C lower than that of **P21a** (Fig. 32). In the cooling run the transparency recovers from 0% to almost 100% at about the same temperature as in the heating run. Apparently recomplexation of the spacer-containing polymer **P22** is significantly faster than that of polymer **P21a**, which contains directly attached adamantyl groups. These results correlate with the degree of mobility of the adamantyl groups attached to the polymer.

In addition, we reported about the behaviour of an LCST copolymer **P23** bearing a covalently attached solvatochromic 4-azastilbene dye and investigated the solvatochromism of this polymer in the presence of Me-β-CD [69].

A characteristic bathochromic shift from orange to dark red could be observed when the aqueous polymer solution at basic pH is heated above the LCST value of about 31°C (Figs. 33 and 34). This means that, during precipitation of the polymer due to heating above the LCST value, most of the polar water molecules are pushed out of the polymer coil. This causes a negative change of polarity next to the dye moiety, which results in a colour change. This temperature-dependent colour change

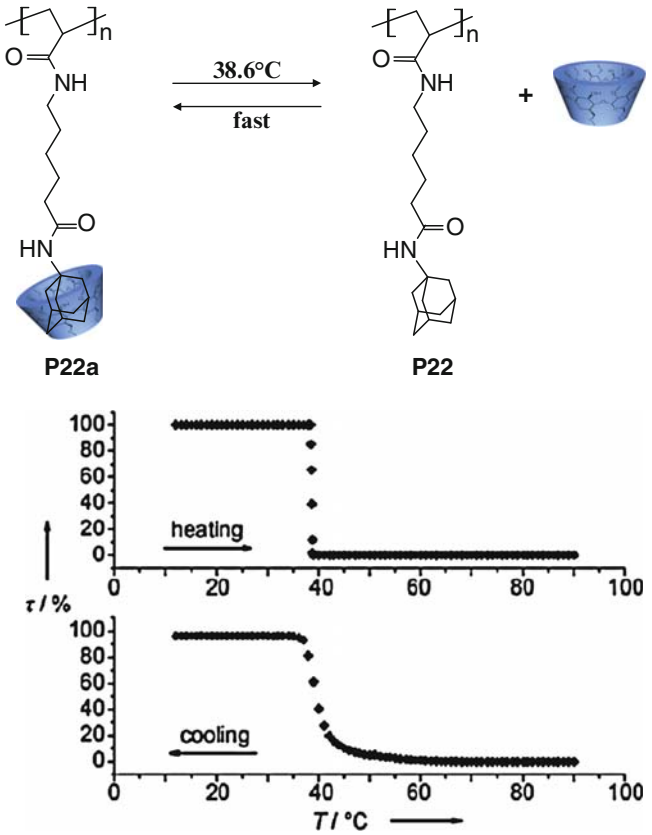


Fig. 32 Rapid complexation of **P22** by Me-β-CD. Transmittance as a function of temperature for an aqueous solution of polymer/Me-β-CD complex **P22a** at a heating/cooling rate of 1°C min^{-1}. [**P22a**] = 100 g L^{-1} (13.75 g L^{-1} polymer, 86.25 g L^{-1} Me-β-CD)

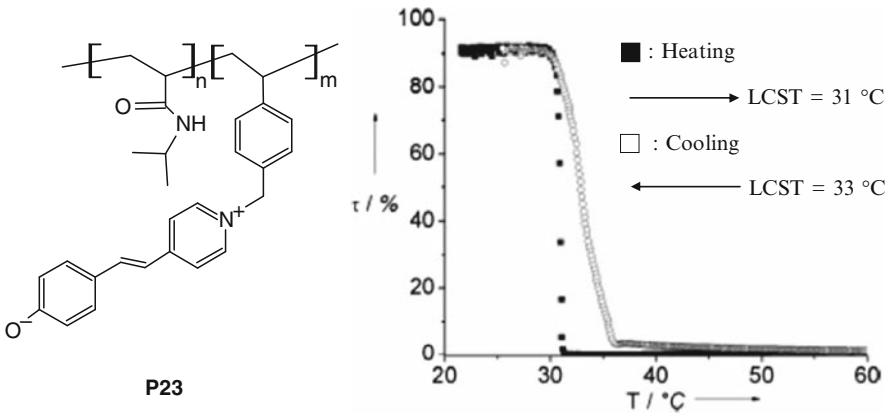


Fig. 33 Transmittance (τ) of a solution of polymer **P23** in water (5 mg mL^{-1}) at pH 10 vs temperature during heating and cooling

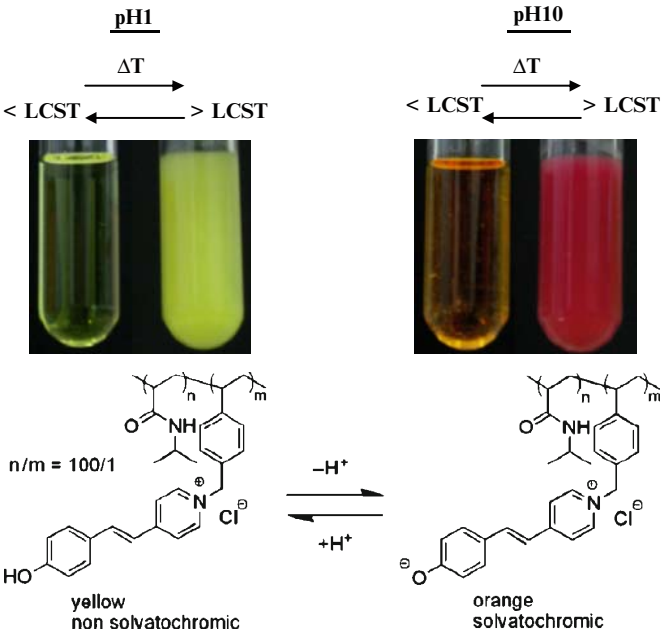


Fig. 34 Colour effects of copolymer **P23** at pH 1 (no shift) and at pH 10 (bathochromic shift)

is fully reversible. However, the protonated copolymer showed no colour change effect due to the solubility change at its LCST.

We clearly found that the bathochromic shift due to negative polarity change was also visible after excessive CD addition to the aqueous polymer solution below its LCST. This means that the complexation of the copolymer **P23** by CD could also be recognized simply by the naked eye.

The unpolar cavity of CD creates an unpolar environment around the dye moiety. The colour change due to CD threading is nearly identical compared to the colour change caused by phase transition. This proves that the dye–dye interaction plays a minor role. As mentioned above, this effect influenced only the deprotonated polymer at high pH. Addition of CD to the polymer solution with the protonated dye (pH 1) showed only a small effect on the visible spectrum. UV measurements started directly after acid addition. Thus, decomposition of CD is not to be expected. This small effect might be due to weak interaction of CD with the protonated dye. In measurements of an aqueous solution of **P23** without CD, glucose was excessively added to this solution to verify the host–guest interactions. As it was expected, no colour change could be detected (Fig. **35 a,**b).

In conclusion, CDs constitute excellent hosts for homo- and copolymerizations. This important property has encouraged the use of CDs in a range of applications related to polymers, as described in this review. These investigations demonstrate the successful application of CDs in polymer synthesis in aqueous medium via free radical polymerization or via a oxidative recombination mechanism. CDs as

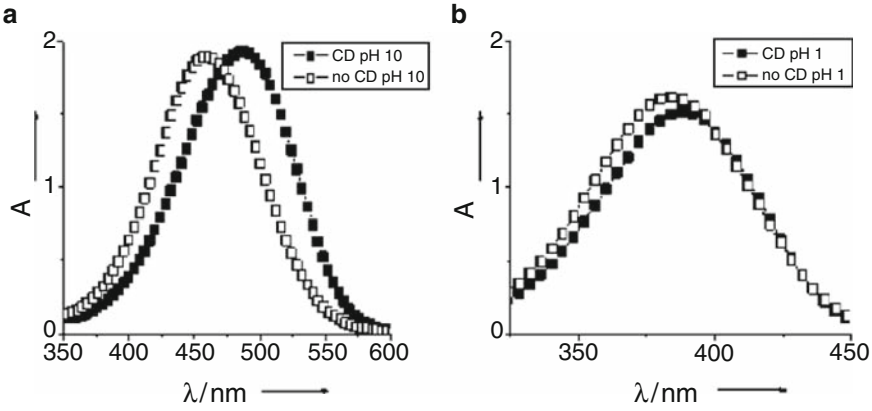


Fig. 35 a,b Visible spectra of a 1.25 g L^{-1} aqueous solution of **P23** with (*filled squares*) (addition of 60 mg of CD) or without (*open squares*) (addition of 60 mg of glucose) at pH 10 **a** and at pH 1 **b**

reaction media are useful to alter both polymerization kinetics and copolymerization-parameters. New aqueous LCST systems can be designed with switchable physical properties.

As expected, within only a few decades an important revolution in the polymer chemistry through CD-mediated reactions might change the current production processes in chemical industry. Undoubtedly, the unique host properties of CDs should be taken into account when novel polymerization processes are created.

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