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# Synthesis and Characterization of Base Labile Poly(*N*-isopropylacrylamide) Networks Utilizing a Reactive Cross-Linker

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Polymer gels possess a broad scientific and technological importance. Especially, water swellable gels, i.e., hydrogels, have been intensively investigated as materials for sustained-release delivery systems,[1] scaffolds for tissue engineering,[2] or separation materials.[3] Of particular interest are hydrogels that exhibit stimuli-responsive behavior, i.e., which respond to an external stimulus, such as temperature,[4−6] pH,[7,8] or salt concentration,[9] by swelling or deswelling.

In this context hydrogels based on poly(*N*-isopropylacrylamide) (PNIPAm) found great interest.[10] PNIPAm features a sharp transition behavior in water in response to temperature changes. This lower critical solution temperature (LCST) appears for PNIPAm in water at 32 °C.[11,12] Besides PNIPAm, a wide range of poly(N-substituted acrylamide)s have been investigated exhibiting a LCST in water. Further examples are poly(*N*-isopropylmethacrylamide),[13] poly(*N,N*-diethylacrylamide),[14] or poly(*N*-cyclopropylacrylamide)[15] featuring a LCST at 38−42, 33, and 57 °C, respectively. Accordingly, PNIPAm hydrogels exhibit a volume phase transition temperature (VPTT) at around the LCST of PNIPAm.[16,17] At temperatures higher than VPTT, the hydrogel undergoes a transition from a swollen (hydrophilic) state to a deswollen (relatively hydrophobic) state. Besides PNIPAm, there have been numerous examples of stimuli responsive hydrogels.[18,19]

Typically, one differentiates two synthetic routes toward chemically cross-linked PNIPAm hydrogels. The first approach addresses the synthesis of hydrophilic PNIPAm copolymers, which consist of a cross-linkable moiety. These polymers can then be cross-linked afterward, resulting in the PNIPAm hydrogel. The advantage of this approach is that structuring and patterning of PNIPAm hydrogels are easily possible. Usually, photo-cross-linking is the method of choice as it can be performed by photodimerization of cinnamoyl,[20,21] coumaroyl,[22] stilbene,[23] or dimethylmaleimide[24,25] derivatives, by decomposition of phenylazido groups[26] or by photoaddition onto benzophenone groups.[27]

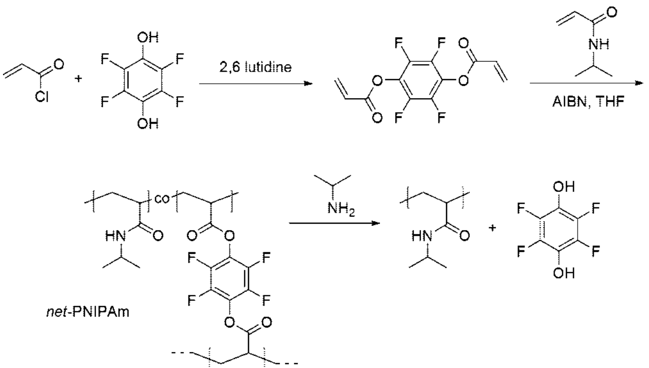
Second, *N*-isopropylacrylamide (NIPAm) can be polymerized in the presence of a cross-linker, e.g., *N,N′*-methylenebis(acrylamide),[28] yielding a PNIPAm hydrogel. Such a polymerization can be performed in solution or in emulsion.[29] However, most hydrogels are based on chemically inert cross-linkers, like the above-mentioned *N,N′*-methylenebis(acrylamide) (MBAa). Only several attempts of chemically labile cross-linkers are reported. Among those, acid labile cross-linkers are dominating, most often based on acetal groups[30−32] or *tert*-butyl esters.[33] Further, a chemically degradable cross-linker, *N,N′*-(1,2-dihydroxyethylene)bis(acrylamide) (DHEA), has been described which can be cleaved in the presence of $NaIO_4$.[34] In contrast to them, base labile cross-linkers are not intensively studied. One example of a base labile cross-linker is a carbamate containing cross-linker, noted by Zhang et al.[35] In another example, the degradation results from the base-catalyzed Lossen rearrangement of substituted hydroxamic acid.[36] To the best of our knowledge, cross-linkers based on activated esters have not yet been investigated as labile cross-linkers. Our previous investigations revealed that pentafluorophenyl acrylate and methacrylate esters can be considered as ideal reactive monomers, which can be polymerized under defined conditions. The resulting polymers are soluble in many organic solvents and are stable against hydrolysis under neutral conditions but react quantitatively with nucleophiles, such as amines or bases.[37−40] This motivated us to investigate a diacrylate based on tetrafluorohydroquinone as a new kind of cross-linker that is expected to react with nucleophiles under cleavage with the potential use as biodegradable hydrogels.

Within this communication, we present such a new chemically labile cross-linker, synthesis of PNIPAm hydrogels thereof, their stimuli-responsive behavior in dependence of temperature, and the chemical cleavage of the hydrogels.

The synthesis of the reactive cross-linker 2,3,5,6-tetrafluoro-1,4-phenylene diacrylate (TFPDA) was done by esterification of acryloyl chloride with tetrafluorohydroquinone in the presence of 2,6-lutidine in dichloromethane (see Scheme 1). Purification by column chromatography yielded colorless crystals in 70%. The reactive cross-linker was characterized by $^1$H NMR, and the spectrum showed the three protons of the double bond as double doublets at 6.70, 6.36, and 6.16 ppm, respectively. Because of the presence of fluorine atoms in the monomer, a $^{19}$F NMR spectrum was recorded, which showed only one sharp signal at −153.62 ppm, corresponding to the four equivalent aromatic fluorines. This is a clear shift in respect to the signal at −166.67 ppm, which is found for the free tetrafluorohydroquinone, thereby indicating the successful formation of the ester on both hydroxy functionalities. Using IR spectroscopy, the activated ester band of the bisacrylate was detected at 1755 cm$^{-1}$, indicating again the formation of an ester. No band for the free OH group was detected, confirming that both hydroxy functionalities of tetrafluorohydroquinone have been transformed into the respective ester group.

For the synthesis of PNIPAm hydrogels, *N*-isopropylacrylamide, different ratios of 2,3,5,6-tetrafluoro-1,4-phenylene dia-

**Scheme 1. Synthesis of the Labile Reactive Cross-Linker, a PNIPAm Hydrogel Thereof, and the Degradation of the Gel Using Isopropylamine**



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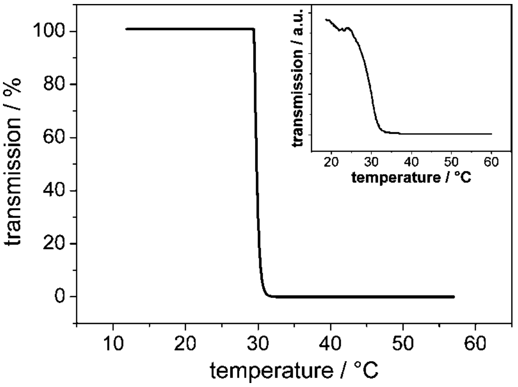

**Figure 1.** LCST curves of hydrogel C (inset) and of the dissolved gel, i.e., linear PNIPAm.

**Table 1. Composition and Swelling Ratios of the PNIPAm Gels**

| | | | | SC/% | | |
|---|---|---|---|---|---|---|
| sample | NIPAm [mmol] | TFPDA [mmol] | NIPAm:TFBA | $H_2O$ (20 °C) | $H_2O$ (45 °C) | THF |
| A | 8.8 | 0.044 | 200:1 | 98 | 75 | 92 |
| B | 8.8 | 0.088 | 100:1 | 90 | 58 | 89 |
| C | 8.8 | 0.176 | 50:1 | 75 | 40 | 85 |
| D | 8.8 | 0.352 | 25:1 | 49 | 5 | 80 |

crylate (TFPDA) (see Table 1) and AIBN were dissolved in THF. After degassing, polymerization was performed at 90 °C for 20 min. The resulting gel was washed several times with THF to extract any remaining monomer and low molecular weight moieties. ATR-IR spectroscopy of the dried gel showed a strong amide band at 1646 $cm^{-1}$, indicating the poly(*N*-isopropylacrylamide) and a weak band at 1776 $cm^{-1}$ due to the ester group of the cross-linker. To characterize the hydrogel, first the swelling−deswelling behavior was investigated. Table 1 shows the swelling behavior of PNIPAm gels that was measured in either distilled water at 20 °C, below LCST and at 45 °C, above LCST or THF as a function of varying amount of cross-linker. The gels were allowed to swell until their weight was constant and were dried afterward in vacuum until constant weight was achieved again. The content of solvent that the gel can uptake in the swollen state was determined by the equation

$$\mathrm{SC}\ (\%) = [[m(\mathrm{Gs}) - m(\mathrm{Gd})]/m(\mathrm{Gs})] \times 100 \qquad (1)$$

with SC the content of solvent, *m*(Gs) the mass of the swollen gel, and *m*(Gd) the mass of the dried gel. Table 1 summarizes the swelling ratios. The degree of swelling is related to the amount of cross-linker incorporated. In agreement with other cross-linkers that have been reported,[41,42] we found that the higher the amount of cross-linker used, the lower the swelling of the gel. However, this tendency is dramatically enhanced for the swelling in water. The swelling of the gel in THF showed only a slight variation between 92% and 80% when the concentration of the cross-linker was changed from 0.5 to 4 mol %. It appears that the observed swelling ratios are slightly higher than those reported for other PNIPAm hydrogels, which might be due to the different reactivity ratios of NIPAm/TFPDA compared to NIPAm/MBAa in the copolymerization.

In the following, the thermal behavior of the hydrogel in water was studied. Because of the LCST behavior of PNIPAm in water, the prepared hydrogels were examined and the VPTT was determined by turbidity measurements. The inset in Figure 1 shows the light transmittance of a 633 nm laser through a PNIPAm hydrogel sample (2 mol % cross-linker) as a function of temperature, with the VPTT to be at 28 °C.

To demonstrate the utility of the 2,3,5,6-tetrafluoro-1,4-phenylene diacrylate as a degradable cross-linker under basic conditions, detailed studies have been performed using the hydrogel D (4 mol % cross-linker). The water-swollen PNIPAm gel was treated with different kinds of nucleophilic agents, such as ammonia solution, sodium hydroxide solution, and different kinds of primary and secondary amines (see Scheme 1). All of the above-listed nucleophiles were able to dissolve the gel immediately, as long as the alkyl rests were not too bulky, as it was the case for diisopropylamine.

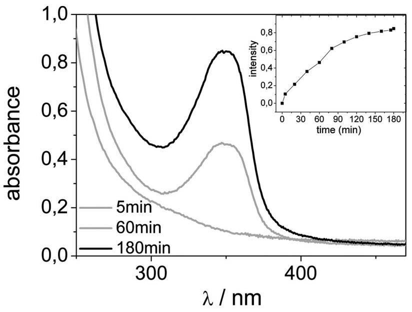

**Figure 2.** UV/vis spectra of the dissolution of hydrogel D carried out in an oxygen atmosphere, recorded at 5, 60, and 180 min. The inset shows the evolution of the intensity at 350 nm with time during the dissolution of hydrogel D with isopropylamine at room temperature.

When the base labile hydrogel was allowed to react with isopropylamine, dissolution of the gel resulted in a soluble linear PNIPAm polymer. The obtained PNIPAm polymer was then analyzed by size exclusion chromatography and a molecular weight of $M_n = 4730$ g/mol with a polydispersity of $M_w/M_n = 1.35$ could be calculated. For the obtained soluble PNIPAm polymer, the LCST was determined by turbidity measurements, and the result is shown in Figure 1. In comparison to the hydrogel, the LCST of the soluble PNIPAm was measured to be 29.7 °C.

During the dissolving process of the hydrogel with a primary amine, tetrafluorohydroquinone is formed as a byproduct. If the reaction was carried out in an oxygen atmosphere, the solution turned from a colorless swollen gel into a deep purple solution, while the gel dissolved. Because of the oxygen present, the hydroquinone is partially oxidized to the quinone, creating a charge transfer complex between the hydroquinone and the quinone. Thus, the color change indicates the dissolution of the previously cross-linked polymer sample. During the dissolution of the gel, UV/vis spectra were recorded and a peak at 350 nm was observed, which increased in intensity with reaction time (see Figure 2). The intensity of the peak reached a constant maximum value after 200 min, indicating a complete dissolution of the gel. Repeating the dissolution experiment of the gel in a nitrogen atmosphere, thus excluding oxygen, did not result in any change of color.

In summary, we were able to prepare a new chemically cleavable cross-linker based on 2,3,5,6-tetrafluoro-1,4-phenylene diacrylate. PNIPAm hydrogels were successfully prepared by radical polymerization using this cross-linker. Hydrogels with different compositions of cross-linker were synthesized, and the degree of swelling as well as the stimuli-responsive behavior with temperature was analyzed. The dissolution of the hydrogels by amines was indicated by deep purple coloration of the resulting polymer solution, due to the oxidation to a quinone, which results in a colored charge transfer complex with the contained hydroquinone. This attendant color change in combination with the advantage of a base labile cross-linker that enables the dissolution of the hydrogel under certain biological conditions may find many applications, e.g., in sensing devices that are based on functional hydrogels or in optical detection of the degradation of a biocompatible hydrogel.

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**Supporting Information Available:** Experimental procedures of the synthesis of 2,3,5,6-tetrafluoro-1,4-phenylene diacrylate and PNIPAm hydrogels formation and degradation. The material is available free of charge via the Internet at http://pubs.acs.org.

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