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Microwave Induced Chain Transfer Polymerization of a Stimuli Responsive Polymer and Determination of Its Critical Solution Temperature

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Abstract

The outlined experiments will provide a simple introduction for undergraduate students to the concepts of living radical polymerisation (telomerisation) and to stimuli-responsive materials, namely those showing a critical solution temperature in aqueous solution. They learn to polymerize and examine an intelligent polymer in a 8 hours, one day laboratory period. The poly-*N*-isopropylacrylamide (PNIPAM) in focus is a thermo responsive polymer with a critical solution temperature (CST) of approximately 32 ºC in pure water. Oligomeric PNIPAM (2000 g/mol) is telomerized with AIBN as initiator and 3-mercaptopropionic acid as chain transfer agent. The reactants are heated by microwave irradiation in a solvent free process, employing a domestic microwave oven with 2.45 GHz magnetron frequency. The isolated telomer contains a single carboxylic function at one end of the polymer chain, allowing precise determination of the average molecular weight by titration with NaOH solution and phenolphthalein as indicator. The critical solution temperature phenomenon (CST) is easily detected by direct observation in daylight or by a temperature programmed UV-VIS spectrometer.

Keywords

Polymer Chemistry, Free Radicals, Materials Science

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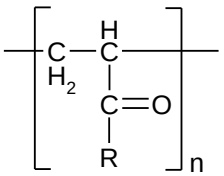
This article details a learning experience, in the synthesis and structure/property examination of a representative example of an intriguing new class of materials, the so-called smart or intelligent polymers. These interesting macromolecules are also known as stimuli responsive and environment sensitive substances. Such molecules are increasingly discussed for applications as varied as drug delivery, artificial muscles, bioseparation [1], homognous catalysis [6], optical switches [7], and even smart paints. Such molecules show pronounced property changes, e.g. changes in solubility/wettability, as a response to a small change in the environment. Depending on the molecule, the stimulus might be a temperature change, the addition of an electrolyte, a pH variation, a light beam, the addition of specific molecules, or combinations thereof. A variety of structures exist, which exhibit this phenomenon preferentially in aqueous solutions. Among the synthetic stimuli-responsive materials poly-(N-isopropylacrylamide), PNIPAM, is currently the most investigated, most likely due the fact that its critical solution temperature, above which the molecule becomes hydrophobic, is in the physiological range (ca. 32°C). Several poly-*N*-alkylacrylamides demonstrate thermoresponsivness, besides the PNIPAM, which is the focus of this article (Table 1).



R	LCST (°C) in H_2O
NH_2	soluble 0-100[a]
$NHCH_3$	soluble 0-100[a]
$NHCH_2CH_3$	82
$NH(CH_2)_2CH_3$	22
$NHCH(CH_3)_2$	32-34
$NH(CH_2)_3CH_3$	insoluble[b]
$NHC(CH_3)_3$	insoluble[b]
$N(CH_3)_2$	soluble 0-100[a]
$N(CH_3)(CH_2CH_3)$	56
$N(CH_2CH_3)_2$	32
$N(CH_2CH_2CH_3)_2$	insoluble[b]

Table 1. LCST of aqueous solutions of poly-*N*-alkylacrylamides. [a)] No LCST between 0 and 100 ºC. [b)] Polymer doesn't dissolve in water.

In addition, such behaviour has been described for poly(alkylether)phosphazenes [2], poly(*N*-vinylcaprolactam), poly(*N*-vinylpyrrolidone) [3] as well as a number of others [4]. Chemists, Biologists, but also material scientists are attracted by the possibilities that will evolve from systematic research of these materials.

Nomenclature

The nomenclature for poly-*N*-Alkylacrylamides is known in two different notations. Beside the systematic chemical name writing an acronym (condenced version) is often easier to be

used. For example poly-*N*-isopropylacrylamide becomes PNIPAM. In this short notation P stands for polymer, *N* for the nitrogen atom, IP for isopropyl, and AM for acrylamide.

Free Radical Telomerization

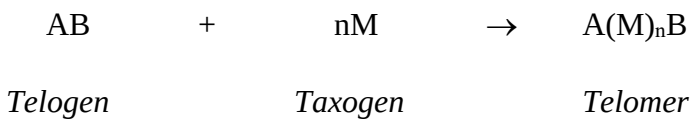
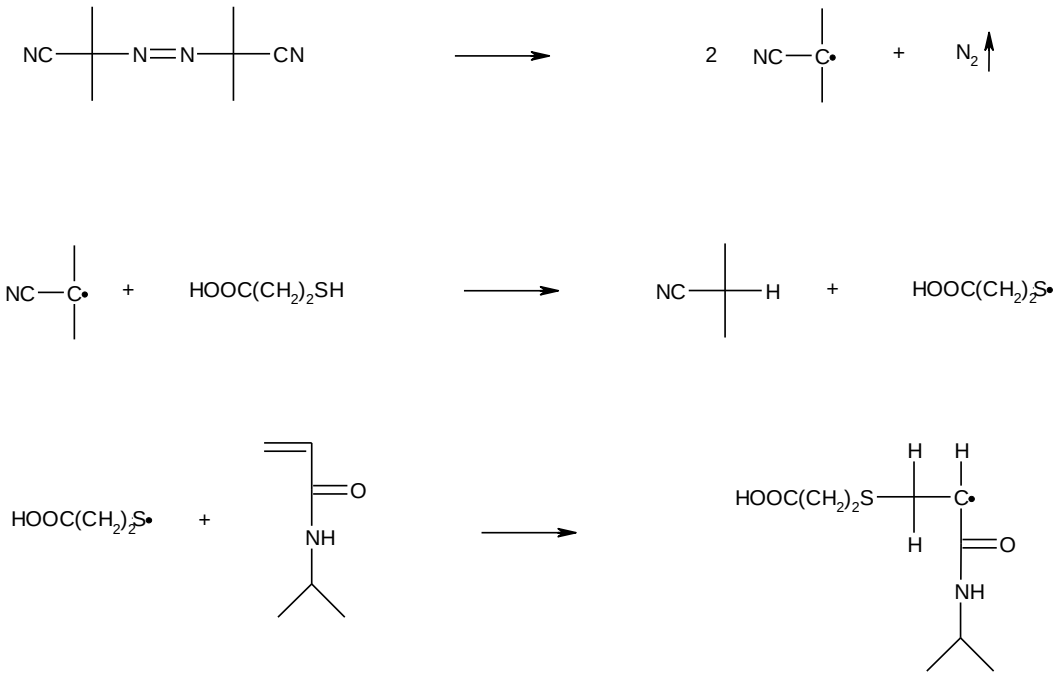


Figure 1. Summary of the telomerization process

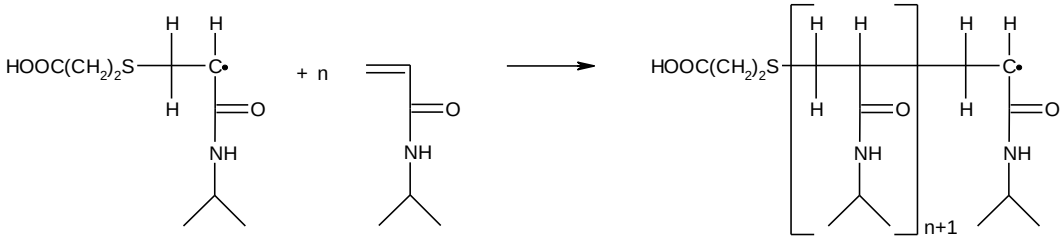
Another concept, which is increasingly becoming important in polymer chemistry is that of controlled radical polymerisation. Whereas standard free radical polymerisation leads to very heterogenous polymers, both in terms of mass and structure, such controlled polymerisation strategies yield highly defined oligomers with molecular weight dispersions of less than 1.2. In this article we intend to introduce the student to such a polymerisation strategy, namely telomerization, also known as radical chain transfer polymerization. This reaction sequence has been applied in polymer science in particular for regulating polymer length. The reaction requires a chain transfer agent (or regulator), which is a reagent with high transfer reactivity. The most efficient ones are mercaptans, such as mercaptopropionic acid.

In the telomerization [8] process (Figure 1) not only are polymers with relatively low molecular weight synthesized, but they also contain only one specific end group. This functional end group is named taxomon (A) and serves usually for further functionalization and molecular weight determination. The product of the telomerization reaction is a *Telomer*, which is also known as a semitelechelic macromolecule. The term semitelechelic means that the polymer has one specific functional end group, while a telechelic polymer (without the prefix semi) contains the same functional end group located at both chain ends [9].

Initiation:



Propagation :



Chain Transfer:

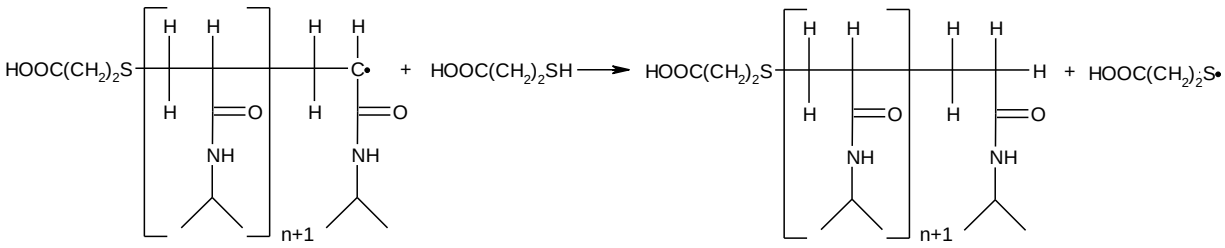


Figure 2. Telomerization mechanism with initiation, propagation and chain transfer step with the initiator (*2,2'*-azobisisobutyronitrile), the monomer (*N*-isopropylacrylamide), and the chain transfer agent (3-mercaptopropionic acid).

Figure 2 illustrates the different steps of a typical teleomerization. The initiator reacts in the initiation step with the *Telogen* ($HOOC(CH_2)_2SH$) and the generated *Telogen*-radical ($HOOC(CH_2)_2S^{\bullet}$) reacts in the following with a *Taxogen* (monomer). Now a chain is initiated and reacts several times with a monomer until a *Telogen* terminates the propagation. The resulting *Telogen*-radical is initiating a new chain (chain transfer). The classical termination reactions by recombination or disproportionation may occur [10] as well, but are unlikely events. Because the chain transfer is a statistical event a polydisperse (non-uniform) polymer is synthesized. Nevertheless the molecular weight distribution should be rather narrow and the polydispersity should be low, i.e. ≤ 1,2.

Critical Solution Temperature (CST)

The critical solution temperature (CST) is the temperature at which a thermo responsive polymer turns insoluble. Above this temperature the macromolecule chain collapse and aggregate, finally to form a solid precipitating coagulate. If the temperature is lowered again below the CST the phase transition is revered and the polymer chains become once more soluble in water. The observed phase transition temperature is also known as cloud point, because the aqueous solution changes from a transparent liquid to a white colloidal solution (Figure 3). Beside the direct observation of the CST by daylight, several measuring

techniques [11] are known to record the phase transition; including UV-VIS, IR, ^{1}H-NMR, and DSC. The CST phenomenon isn't entirely understood and physical chemists try to learn more about the phenomenon by computer simulations. But an obvious fact is that the material properties change from hydrophilic to hydrophobic.

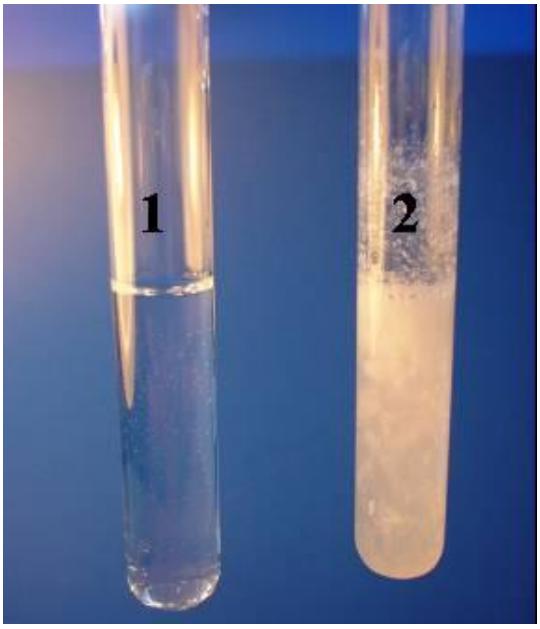


Figure 3. Tube **1** contains an aqueous solution of PNIPAM at room temperature. Tube **2** the same solution heated above 32 °C, shows the CST phenomenon.

Experimental Procedure

Figure 4. Microwave induced telomerization of PNIPAM initiated by AIBN using 3-mercaptopropionic acid as chain transfer agent.

Synthesis: *N*-Isopropylacrylamide, 3-mercaptopropionic acid, and AIBN (2,2'-azobisisobutyronitrile) are weighed into a flask. The mixture is irradiated at 350 watt for 150 seconds in a microwave oven. After cooling the cold glasslike material is dissolved in acetone and then precipitated by adding hexane.

Determination of the molecular weight: Because the taxomon contains a carboxylic acid function the average molecular weight (or molar mass) is easily determined by end group titration. A second technique to determine the average chain length is Maldi-TOF Mass Spectrometry.

Verfication of the structure: This is best done by H-NMR at 200 MHz (600 MHz for fine structure).

Determination of the CST: Two methods may be used to quickly determine the critical solution temperature. With the direct observation by daylight no spectrometer is needed and especially for NIPAM this constitutes a simple yet very reliable methodology for an undergraduate laboratory. In the second, more sophisticated method a UV-VIS Spectrometer with a temperature programmer is required. The CST is read from the inflection point of the curve that results when absorption is plotted versus temperature.

Results and Discussion

As a result of the outlined experiments, a substance is prepared, which is soluble in cold water and precipitated from water hotter than 32°C. A more sophisticated determination of the cloud point temperature by UV/VIS spectroscopy, yielded the turbidity curve shown in Figure 5, which shows the expected phase transition at 32.5°C.

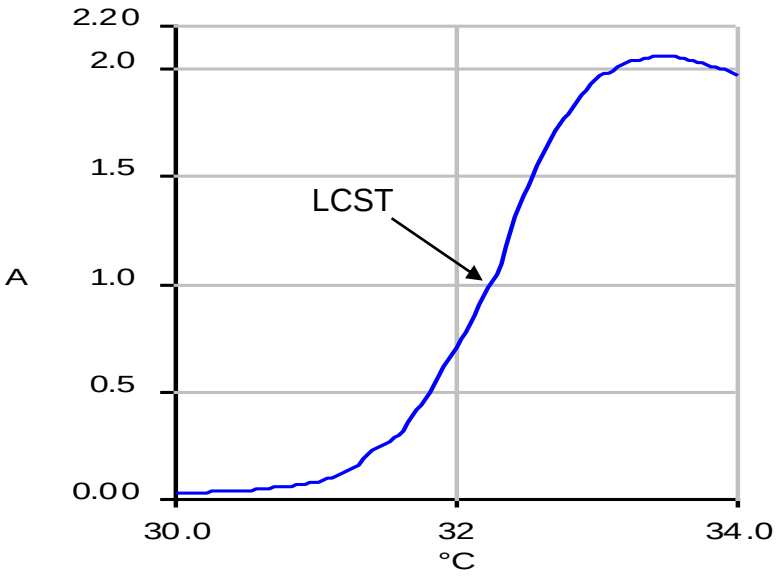


Figure 5. UV-VIS spectra of 10 mg PNIPAM in 1 ml H_2O measured with a temperature gradient of 0.5 °C / min.

The substance was subsequently subjected to further characterization. For structure elucidation ^{1}H-NMR and Maldi-TOF mass spectroscopy were used. ^{1}H-NMR proton spectra were recorded in $CDCl_3$ on an AC BRUKER 200 MHz Spectrometer. The spectra (see Figure 6 for an example) shows a broad singlet at 1.1 ppm (-CH_3) a second broad singlet appears on lower field at 4.0 ppm. The CH and CH_2 group of the backbone are to be found between 1.5 and 2.9 ppm as very broad peaks.

The spectra therefore confirm the expected structure (PNIPAM).

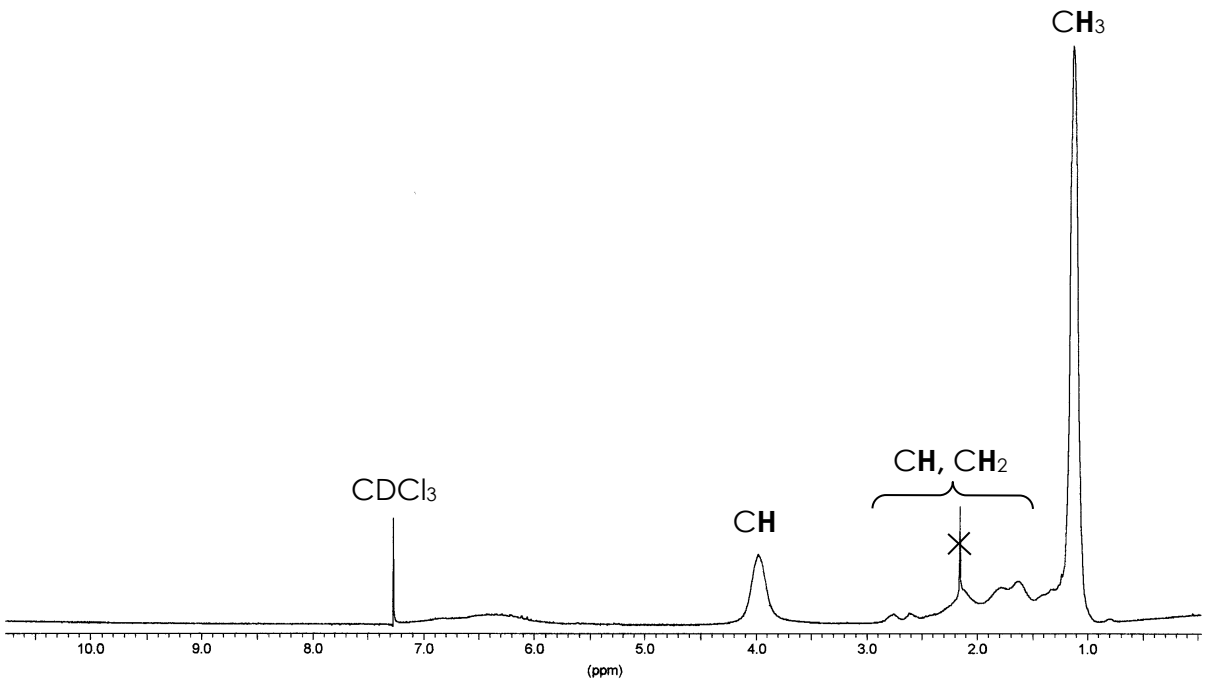


Figure 6. 200 MHz ^{1}H-NMR spectra of poly-*N*-isopropylacrylamide in $CDCl_3$.

Time of flight mass spectroscopy is a versatile tool to analyse short polymers [12] (Figure 7), such as poly-*N*-isopropylacrylamide synthesized here by telomerization (~2000 g/mol). For the measurement the sample compound is mixed with a suitable matrix (often a cinnamic acid derivative) and subjected to laser light. The energy is captured by the matrix and transferred to the sample molecules, which desorbs and are accelerated in an electric field. The mass of the sample molecules is determined by the time of flight required for it to reach the detector. Each peak in the spectra represents the relative abundance of that particular chain length oligomer species in the sample.

In our case the most intensive peak has a molecular mass of 1918.2. Subtracting the molecular weight of 3-mercaptopropionic acid (106.14) and dividing the resulting mass by 113.16 (*N*-isopropylacrylamide mass) one finds that this polymer chain is build of 16 monomer units. From peak to peak an expected distance of 113.16 mass units is found. The additional peaks

of lower intensity, also seen in the spectrum, stem from fragments, which may have attached a molecule of the matrix material. Because complexed chains may also be transferred into the flight tube, especially with high laser power, it is important to adjust laser power to a desirable threshold. Based on the difficulties to record a noiseless spectrum it is equally not simple to find the correct average mass by Maldi-TOF MS. In our spectrum an asymmetric peak distribution is recorded which may mirror a real uneven distribution caused by the telomerization experiment or by the fact that higher molecular weight polymer chains are more strongly retained in the matrix and therefore not as easily moved into the flight tube as shorter chains. The molecular weight determined by MALDI MS was essentially verified by the end group titration, which gave a mass of 1938 g/mol.

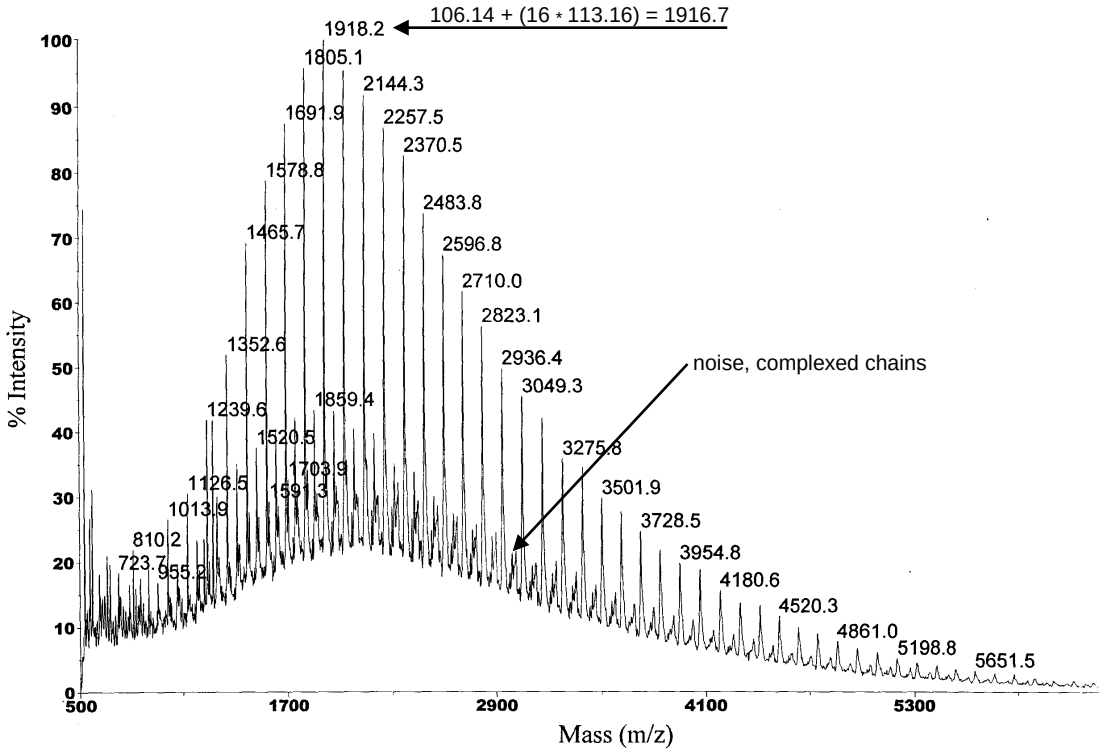


Figure 7. Maldi-TOF mass spectra of poly-*N*-isopropylacrylamide.

Hazards

N-Isopropylacrylamide, 3-mercaptopropionic acid and AIBN are toxic reagents and have to be handled in a fume hood. In addition students need to wear gloves, safety goggles, and other protective clothing.

Microwave radiation is harmful to tissue and only a technically controlled oven should be employed. Because irritant fumes may escape during the synthesis the apparatus has to be installed in a fume hood with efficient ventilation and a protective shield.

Conclusions

Students learn in a quick and instructive approach to telomerize poly-*N*-isopropylacrylamide and analyze it with simple to sophisticated methodologies. The described telomerization procedure is highly reproducible and the isolation rather simple. Thanks to the specially developed protocols (microwave induced synthesis, end group titration, and CST determination in daylight); synthesis, isolation and characterisation is possible in a one-day laboratory session of 8 hours. For advanced students UV-VIS, ^{1}H-NMR, and Maldi-TOF Mass Spectroscopy are options to satisfy their curiosity.

Acknowledgments

The under graduate students from the University of Geneva and the undergraduate students of the Hochschule Wallis are acknowledged for their hard work.

Supplemental Material

Detailed experimental descriptions are available in this issue of *JCE Online*.

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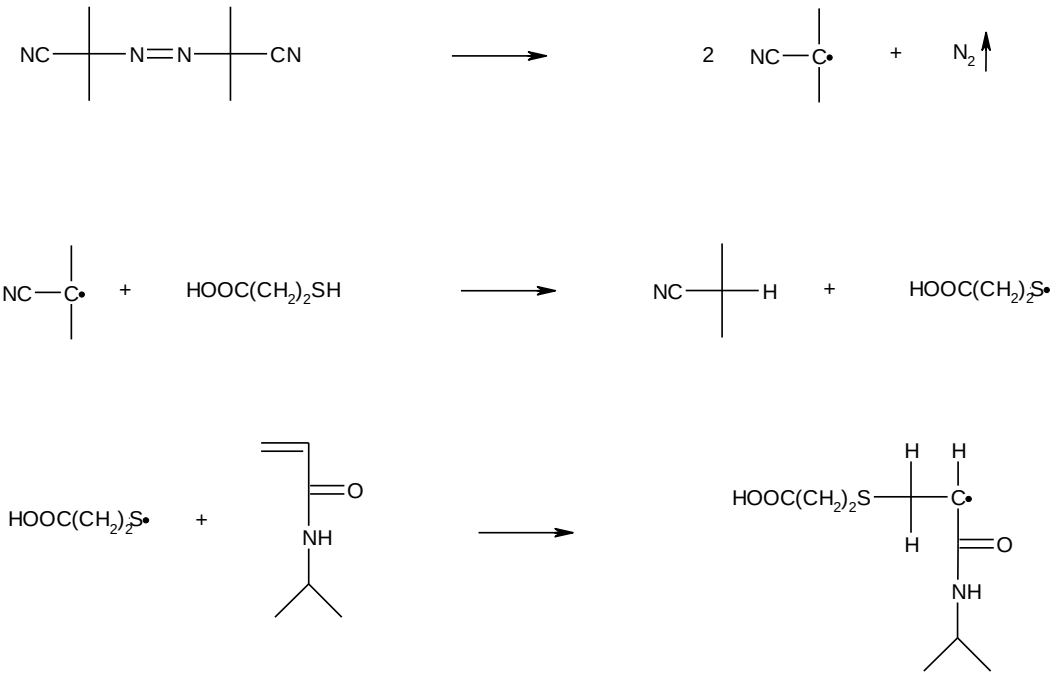
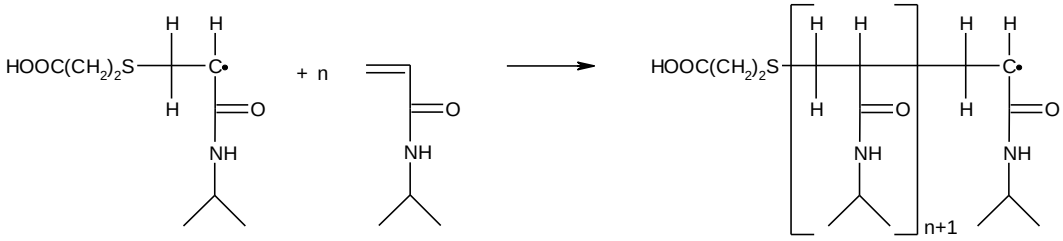
AB	+	nM	→	$A(M)_nB$
Telogen		*Taxogen*		*Telomer*

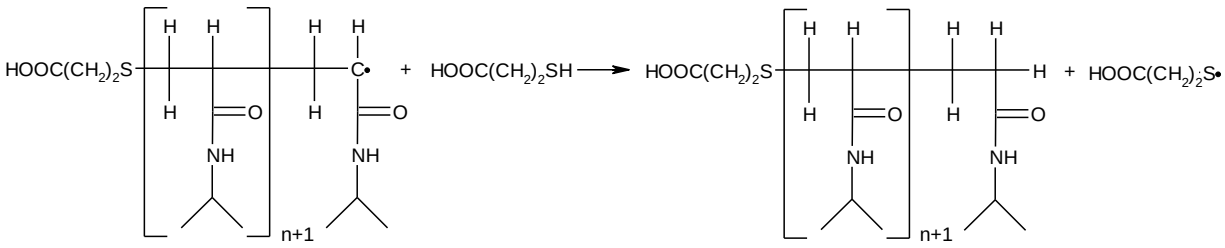
Initiation:

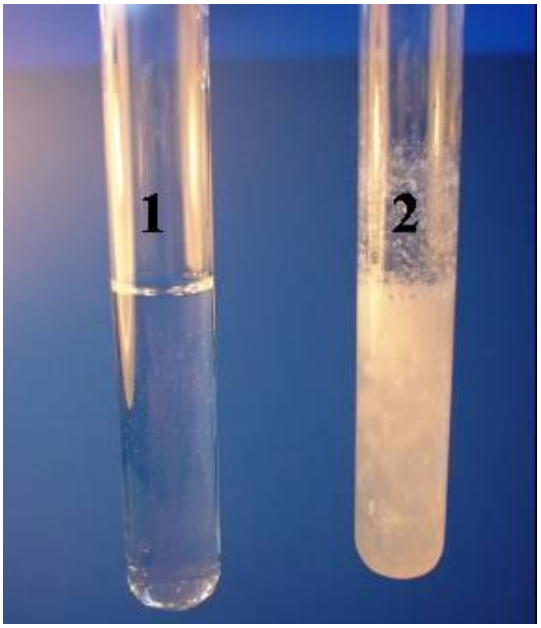


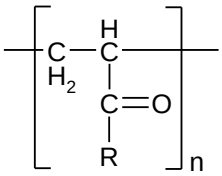
Propagation :



Chain Transfer:




1
2



R	CST (°C) in H_2O
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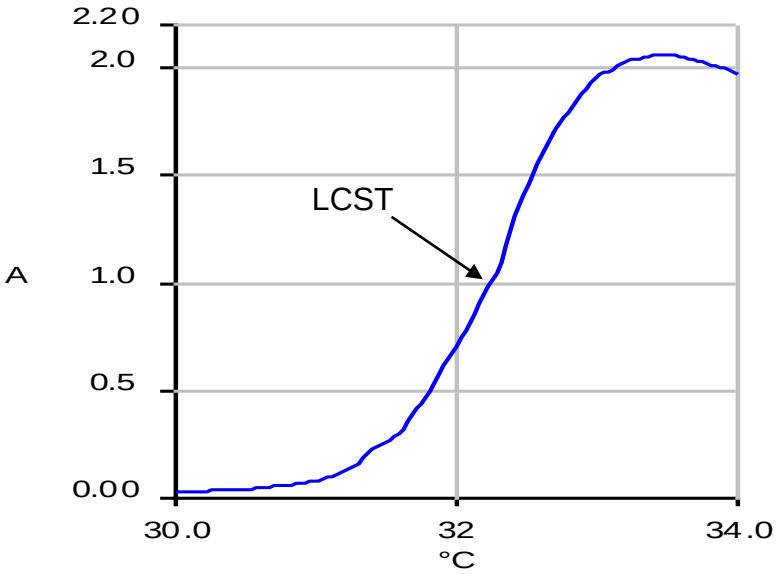
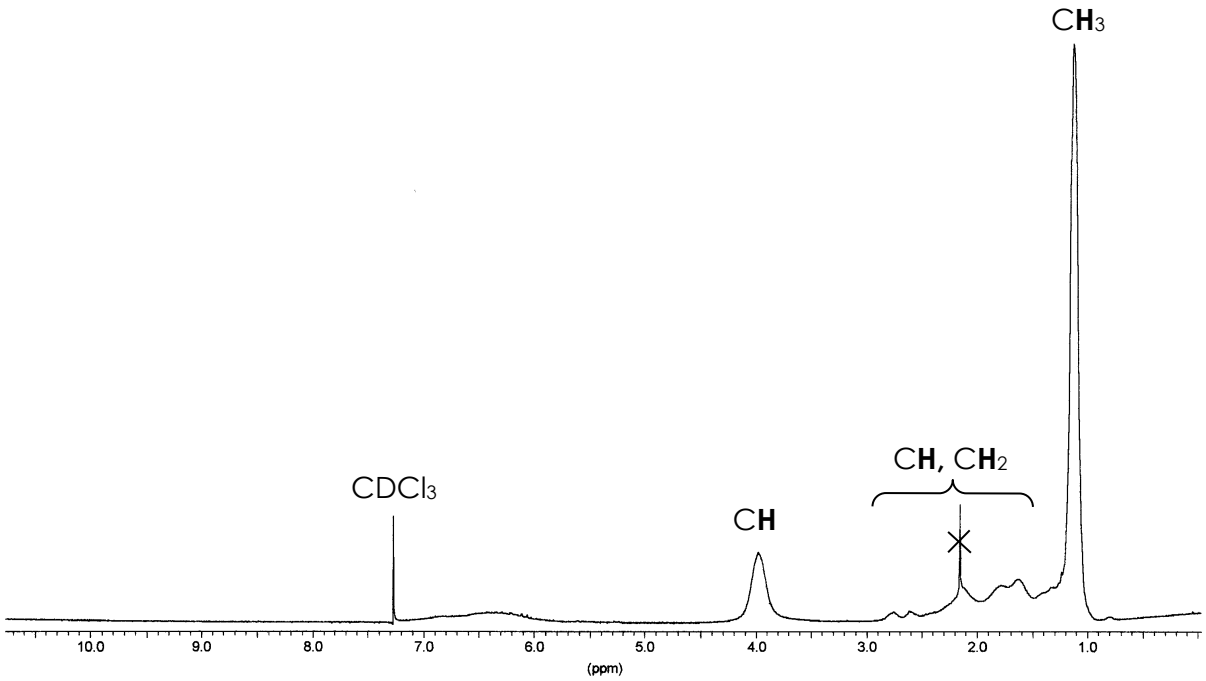
$NHC(CH_3)_3$	insoluble[b]
$N(CH_3)_2$	soluble 0-100[a]
$N(CH_3)(CH_2CH_3)$	56
$N(CH_2CH_3)_2$	32
$N(CH_2CH_2CH_3)_2$	insoluble[b]

Table 1. LCST of aqueous solutions of poly-*N*-alkylacrylamides. [a)] No LCST between 0 and 100 ºC. [b)] Polymer doesn't dissolve in water.


O
HN
+
HOOCCH2CH2SH
AIBN
mw: 350 w, 150 s
HOOCCH2CH2S
C
H2
H
C
H
O
HN
n


2.20
2.0
1.5
1.0
0.5
0.00
A
LCST
30.0
32
34.0
°C


CH3
CDCl3
CH
CH, CH2
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

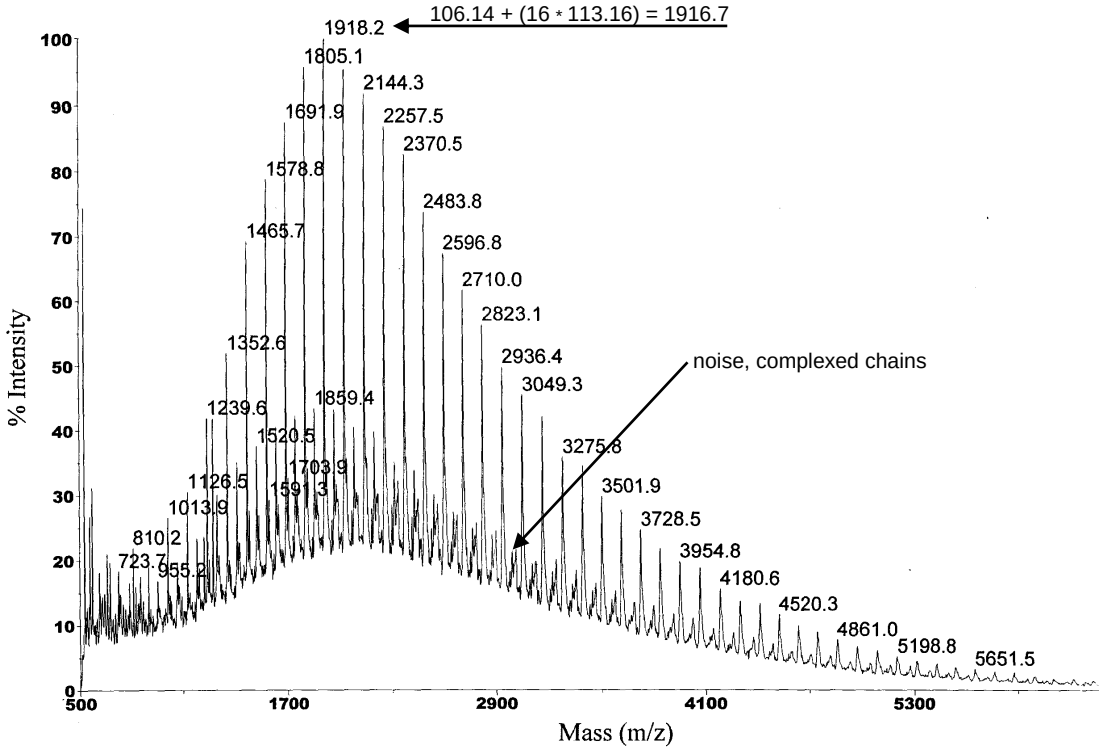

106.14 + (16 * 113.16) = 1916.7
1918.2
1805.1
2144.3
1691.9
2257.5
2370.5
1578.8
2483.8
1465.7
2596.8
2710.0
2823.1
1352.6
2936.4
noise, complexed chains
3049.3
1239.6
1859.4
1520.5
3275.8
1703.9
1126.5
1591.3
3501.9
1013.9
3728.5
810.2
3954.8
723.7
955.2
4180.6
4520.3
4861.0
5198.8
5651.5
% Intensity
Mass (m/z)
100
90
80
70
60
50
40
30
20
10
0
500
1700
2900
4100
5300

Figure 1. Summary of the telomerization process

Figure 2. Telomerization mechanism with initiation, propagation and chain transfer step with the initiator (*2,2'*-azobisisobutyronitrile), the monomer (*N*-isopropylacrylamide), and the chain transfer agent (3-mercaptopropionic acid).

Figure 3. Tube **1** contains an aqueous solution of PNIPAM at room temperature. Tube **2** the same solution heated above 32 °C, shows the CST phenomenon.

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Figure 6. 200 MHz ^{1}H-NMR spectra of poly-*N*-isopropylacrylamide in $CDCl_3$.

Figure 7. Maldi-TOF mass spectra of poly-*N*-isopropylacrylamide.

Supplemental Material for online data base

Instructor notes

Poly-(N-isopropylacrylamide), PNIPAM, is a very interesting molecule. It is a so-called stimuli-responsive or 'smart' material that responds with a pronounced change in behaviour (here water solubility/wettability) in response to a small environmental stimulus (here a small change in temperature). In addition, PNIPAM is easy to synthesize and the reaction can therefore serve as a good introductory experiment to familiarize students with various aspects of polymer chemistry. The product remains stable under ambient conditions for at least three years. In literature it is often suggested to recrystalise the initiator (AIBN) before use, but this is not absolutely necessary, although it may be interesting for the students to learn this technique of initiator preparation. PNIPAM can be prepared under standard conditions (methanol reflux/760 torr). However, the use of a household microwave oven will not only speed up the reaction, but will also add some fun to the experiment. Should there be no microwave oven available, the experiment can carried out in superheated methanol employing an autoclave. This processing is also very reliable in comparison to standard reflux conditions, which are sometimes difficult to control for undergraduate students.

It is recommended that the instructor demonstrates the stimuli-response phenomenon (critical solution temperature) in the pre laboratory session. One needs to heat a polymer solution (10 mg/mL using pure water as solvent) in a glass vial and show the phase transfer by video system or the overhead projector. Another possibility is to enclose the polymer solution in a sealed glass tubing (thin walls and small diameter tubings will improve heat transfer) and to have two glasses of water – one ice cold, the other very hot – ready. Transferring the tube with the polymer solution from one glass to the other can quickly demonstrate the CST phenomenon. In this context it is helpful that the precipitation of PNIPAM occurs quickly

(less than a second) and within a temperature interval of only a few degrees centigrade. Since the precipitation/phase transition is fully reversible, the tubing with the polymer solution can be transferred back and forth between the hot and cold water and thereby made to go through several precipitation / redissolution cycles.

Telomerisation in superheated methanol

(The following procedure is only mentioned for instructors use.)

Telomerisation of NIPAM in superheated methanol (100°C) is simplest done in an autoclave. In this autoclave 350 μL (4 mmol) 3-mercaptopropionic acid, 82 mg (0,5 mmol) AIBN (2,2'-azobisisobutyronitrile), 100 mmol *N*-isoproylacrylamide and 15 mL methanol are mixed together, afterwards the autoclave is sealed. The autoclave is submersed into a heated oil bath (100°C). Some measure has to be taken to allow for easy and safe immersion but also retrieval of the autoclave from the oil bath. We used for this purpose two wires with handles that were wrapped around the autoclave. In addition, the 2 mm thick wires prevented the metallic autoclave from coming into direct contact with the heating plate. After one hour the reaction is over and the autoclave may be removed from the oil bath and cooled by cold water. The workup procedure is the same as described below for the microwave experiment.

Chemicals	3-Mercaptopropionic acid	107-96-0
	N-isopropylacrylamide	2210-25-5
	AIBN (2,2'-azobisisobutyronitrile)	78-67-1
	NaOH	
	Phenolphthalein	77-09-8
	Acetone	
	Hexane	

Lab Supplies:

1) Weigh-boats
2) 50 mL flask
3) 100 mL glass beaker
4) microwave oven (Easy Tronic MO 201) A simple microwave oven as one uses at home works well, but one should be able to adjust the power.
5) 500 mL flask
6) Rotavaporator (Büchi)

Questions and answers to the questions

Questions:

1) Why is it important to carry out the titration of PNIPAM at low speed?

The PNIPAM produced in our experiment has a molecular weight of 2000 g/mol in average. This is small for a polymer molecule, but is nevertheless a big molecule (macromolecule), which carries only a single carboxylic acid group per polymer chain. Therefore your sample is to be considered as highly diluted in regard to the available

carboxylic groups. In addition, the molecule is relatively bulky and this also slows down the titration.

2) Why is the PNIPAM produced in the experiment called a telomer, what is the advantage of such telomers over conventional PNIPAM polymers?

A telomer is produced by telomerisation, also called chain transfer polymerization. The extension of the polymer chain is formed by the telogen (end group former) AB, in our case mercaptopropionic acid $HSCH_2CH_2COOH$. At one end of the final telomer we find the extension in the form of an $-SCH_2CH_2COOH$ group and at the other end of the telomer chain we find the hydrogen atom of the mercaptopropionic acid.

A considerable advantage of this procedure is the fact that we find a specific end group (in our case, for example, the –COOH group) and that this group is reactive and can be made to react (after activation) with other chemical groups such as an amino group ($-NH_2$). Amino groups are found in many biologicals such as proteins and a large number of smart bioconjugates have been prepared comprising of PNIPAM and a protein / peptide. Such bioconjugates are increasingly used for application in biocatalysis, bioseparation or drug delivery. PNIPAM prepared by standard radical polymerization, on the other hand, completely lacks groups that are easily activated for coupling reactions.

3) How do microwaves heat the reaction mixture? Are the employed substrate molecules well suited for this type of heating?

Microwaves interact with dipolar structures in molecules. In the microwave field the dipoles of such molecules are aligned with the field. If one starts to switch the field into the opposite direction with high frequency the molecules start to rotate, which will result in rapid ('dielectric') heating.

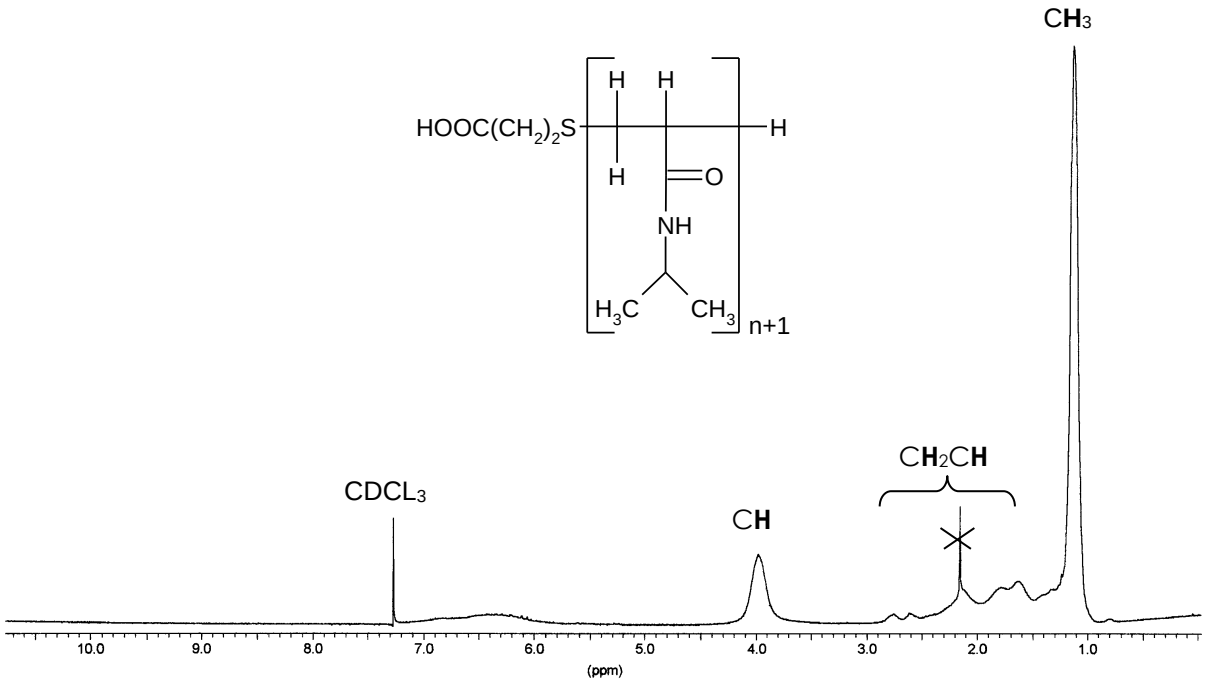
In our experiment all chemicals (monomers, chain transfer agent, and initiator) involved contain dipolar bonds and therefore microwave induction is a very appropriate way to heat the reaction mixture for this process.

4) A) The signals in the ^{1}H-NMR spectrum, see figure below, are broad, what is the reason for this phenomenon?

   B) Assign the signals. The ^{1}H-NMR spectrum was recorded at 200 MHz in $CDCl_3$.

   A) *This is due to the fact that an individual telomer preparation is actually made up from many different molecules of different size. The protons of the groups in each molecule produce their particular chemical shift, which overlaps with many others to give the 'broad' signals.*

   B)



Student notes

Introduction

This laboratory experiment will provide a simple introduction to the concepts of living radical polymerisation (telomerisation) and to stimuli-responsive ('smart') materials, namely those showing a critical solution temperature in aqueous solution. You will learn to polymerise and characterise a smart polymer in a one-day laboratory period. The poly-*N*-isopropylacrylamide (PNIPAM) in focus is a thermo-responsive polymer with a critical solution temperature (CST) of approximately 32 ºC in pure water. Oligomeric PNIPAM (2000 g/mol) is telomerised using AIBN as initiator and 3-mercaptopropionic acid as chain transfer agent. The reactants are heated by microwave irradiation in a solvent free process, employing a domestic microwave oven with 2.45 GHz magnetron frequency. The isolated telomer contains a single carboxylic function at one end of the polymer chain, allowing precise determination of the number average molecular weight by titration with NaOH using phenolphthalein as indicator. The critical solution temperature phenomenon (CST) is easily detected by direct observation in daylight or by a temperature programmed UV-VIS spectrometer.

In this laboratory you are requested to:

a) synthesise poly-*N*-isopropylacrylamide
b) characterise the polymer by titration (determination of the number average molecular weight)
c) determine the CST (critical solution temperature)
d) answer the additional questions

a) Preparation of Poly-*N*-isopropylacrylamide

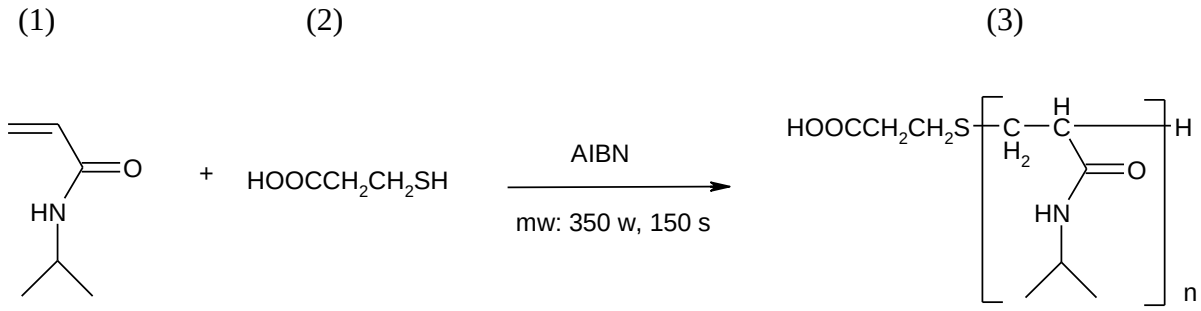


Figure 1. Microwave induced telomerisation of *N*-isopropylacrylamide (1) initiated by AIBN using 3-mercaptopropionic acid (2) as chain transfer agent and resulting in poly-*N*-isopropylacrylamide bearing a carboxylic acid end group (3) as final product.

5.65 g (50 mmol) *N*-isopropylacrylamide, 175 µL (2 mmol) 3-mercaptopropionic acid, and 41 mg (0,25 mmol) AIBN (2,2'-azobisisobutyronitrile) are weighted into a 50 mL one-neck flask. The open flask is placed in a 100 mL glass beaker installed on the rotating plate of the microwave oven (Easy Tronic MO 201, but any other microwave oven with power control will serve). The flask with the reaction mixture should be preferentially placed close to the rim of the rotating plate to enhance homogeneous microwave irradiation. The mixture is heated at 350 Watt for 150 seconds. The very hot transparent, slightly yellow gel is allowed to cool to room temperature. After cooling the material becomes glasslike. 50 mL acetone is added and by shaking, if necessary by additional grinding with a spatula, the material is slowly dissolved. The pale yellow solution is transferred to a 500 mL flask and 250 mL hexane is added. The PNIPAM should quickly precipitate and the supernatant solution can be decanted. To improve the purity of the PNIPAM, the dissolution/precipitation procedure should be repeated at least once. Finally a pure white product is obtained that is redissolved in 50 mL acetone. With a rotavaporator (25 mbar / 50 °C) the solvent is slowly removed and the

product can be found distributed over the inner glass wall of the flask as a porous white foam (2-4 mm thick). With high vacuum (10^{-3} mbar / 25 ºC, one hour) the polymer can be dried to completeness.

Caution:
The mercaptopropionic acid has a bad odour (thiol group), therefore weigh this compound under the hood. Place the microwave oven also in a hood, because some mercaptopropionic acid will always escape during the reaction. Never close the flask in which the reaction takes place, it may explode. Place a protective shield in front of the oven. Wait some time to remove the reaction flask from the oven after the irradiation, because it becomes very hot.
Don't keep the flask with the product in your hands while grinding with your spatula to dissolve the glass like polymer. Even thick glass may break and there is a risk of injury. It may take some time until the polymer is completely dissolved, remain patient.

b) Characterization of the polymer molecular weight by end group titration

Because PNIPAM telomers contain a carboxylic acid end group, the number average molecular weight is easily determined by titration of a known quantity of the telomer.
For the average molecular weight determination 100 mg of the polymer are dissolved in 3 mL H_20 and cooled in an ice bath (ca. 3 °C). A little phenolphthalein is added and the solution is titrated with 0.01 M NaOH until the indicator turns to purple (low speed titration). A second technique to determine the average chain length is MALDI-TOF[1] mass spectrometry.
MALDI-TOF mass spectroscopy is only possible with the help of an instructor. Ask if you are assigned to carry out this experiment.

[1] MALDI-TOF: Matrix-Assisted-Laser-Desorption/Ionization Time-of-Flight

Procedure for Mass Spectroscopy with a MALDI-TOF System

It is possible to record the MALDI TOF mass spectra with a PerSeptive Biosystems Voyager-DE STR instrument equipped with a 2-meter ion flight tube and delayed extraction system. However, any other system of similar design may also serve. A solution of 10 mg/mL 3,5-dimethoxy-4-hydroxycinnamic acid and a solution of 30 % CH_3CN and 0.1 % trifluoroacetic acid were mixed with the sample. 1 μL of the mixture was loaded on a gold target plate and allowed to dry. The spectra were obtained in the linear mode (20 kV accelerating voltage) using a nitrogen laser at 337 nm for irradiation. 256 scans were recorded. External calibration was performed with horse myoglobin under the same conditions.

c) CST-Measurements

Two methods may be used to define the critical solution temperature of the PNIPAM in water. With the direct observation by daylight no spectrometer is needed. In the case of PNIPAM, which shows very quick and abrupt precipitation, this is a very reliable method. For the measurement, 20 mg of PNIPAM are dissolved in 1 mL of distilled water. This solution is best prepared directly in a 4 mL glass vial with screw cap and a magnetic stirring bar. The vial is then placed in a temperature controlled water bath (a glass beaker on a heating plate with electronic temperature control device is a good solution). The measurement is started at room temperature and performed with a temperature gradient of 0.5 °C / min.

In the second method a UV-VIS Spectrometer such as the Perkin Elmer Lambda 20 equipped with a Peltier Temperature Programmer PTP-6 is used. 10 mg PNIPMA are dissolved in 1 mL of distilled water and pipetted into a semi micro quartz cuvette. The optical density of the solution is followed at 500 nm as a function of the temperature at a heating rate of 0.5 ºC / min. The critical solution temperature corresponds to the point of inflection of the recorded turbidity curve.

d) Additional Questions:

1. Why is it important to carry out the titration of PNIPAM at low speed?
2. Why is the PNIPAM produced in the experiment called a telomer, what is the advantage of such telomers over conventional PNIPAM polymers?
3. How do microwaves heat the reaction mixture? Are the employed substrate molecules well suited for this type of heating?
4. A) The signals in the ^{1}H-NMR spectrum, see figure below, are broad, what is the reason for this phenomenon?

   B) Assign the signals. The ^{1}H-NMR spectrum was recorded at 200 MHz in $CDCl_3$.