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(54) Title: AN INITIATOR OF ATRP RADICAL POLYMERISATION, A METHOD OF ITS SYNTHESIS, AND A METHOD OF SYNTHESIS OF LOW-DISPERSION POLYMER AND COPOLYMER USING THIS INITIATOR

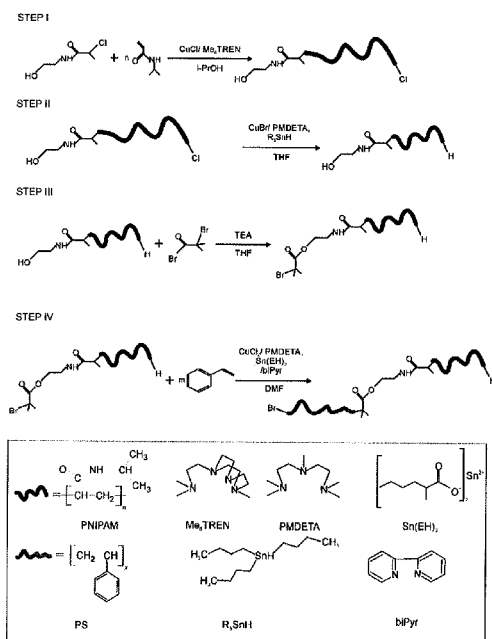


Fig. 3

(57) Abstract: An initiator of ATRP radical polymerisation having a functional group with a substituent active in polymerisation process, is characterised in that it is a bifunctional initiator containing at least two functional groups separated by a hydrocarbon moiety Y, where the first functional group has an active substituent X and the second functional group has a protecting group Z, which can be chemically modified with the same or a different substituent than the active substituent X present in the first functional group. A method of synthesis of 2-chloro-N-(2-hydroxyethyl)propionamide initiator, NCPAE, is characterised in that ethanolamine is subjected to an acylation reaction with 2-chloropropionyl chloride in presence of triethylamine (TEA), wherein the reaction is carried out under inert atmosphere at room temperature.

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An initiator of ATRP radical polymerisation, a method of its synthesis, and a method of synthesis of low-dispersion polymer and copolymer using this initiator

Subject of this invention is an initiator of controlled radical polymerisation ATRP (*Atom Transfer Radical Polymerisation*) for synthesis of low-dispersion polymers and block copolymers, including thermosensitive polymers and copolymers, method of its synthesis, and the use of this initiator in polymerisation reactions.

Thermosensitive polymers are known, *i.e.* those that show a change in their chemical and physical properties at a certain temperature (defined as phase transition temperature, PTT) [*Prog. Polym. Sci.* 32 (2007) 1205]. One of the most intensively studied thermosensitive polymers is poly(N-isopropylacrylamide) (PNIPAM), due to its biocompatibility, and the fact, that PTT of this polymer is close to human body temperature. As a result, PNIPAM-containing materials can have many medical applications, among others, as carriers for controlled drug release, base materials in tissue engineering, and new carriers in gene therapies [*Polymers*, 3 (2011) 1215].

A block copolymer composed of poly(N-isopropylacrylamide) (PNIPAM) block and polystyrene (PS) block, PNIPAM-*block*-PS, is known, which macromolecules exhibit simultaneously thermosensitivity due to the presence of the PNIPAM block, and amphiphilicity due to the presence of two fragments with an opposite affinity for water: a hydrophilic PNIPAM block and a hydrophobic PS block. Due to this structure, PNIPAM-*block*-PS copolymers have an ability to self-assemble into thermosensitive nanostructures such as micelles, inverted micelles, liposomes and others. Systems of this type can be successfully used for controlled drug release and for other biomedical purposes [*Prog. Polym. Sci.*, 34 (2009) 893]. Due to the widespread use of PS as a biocompatible material in cell cultures, PNIPAM-*block*-PS copolymers may also find applications in this field.

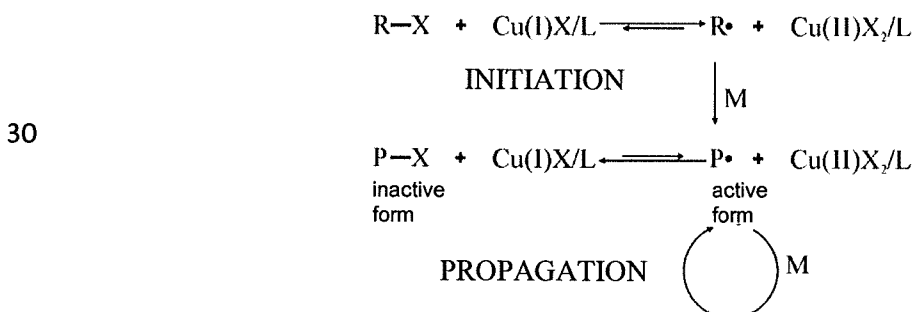
Controlled radical polymerisation (CRP) methods are known for producing low-dispersion homopolymers as well as copolymers with narrow molecular weight distributions and well-defined architecture, *i.e.* block, gradient, and star copolymers [*Polimery*, 56 (2011) 427; "*Progress in Controlled Radical Polymerisation: Mechanisms and Techniques*" by the American Chemical Society (2012)]. The most important techniques used in CRP include stable free radical polymerisation (SFRP), reversible addition-fragmentation transfer polymerisation (RAFT), and atom transfer radical polymerisation (ATRP) [*Prog. Polym. Sci.* 38 (2013) 63; *Polym. Chem.* 9 (2018) 2532; *Chem. Rev.* 101 (2001) 2921]. Among them, particularly advantageous is the ATRP due to its applicability for a wide group of monomers and the possibility of obtaining polymers

with a very narrow molecular weight distribution (PDI below 1.5), as well as planned-architecture copolymers, *i.e.* block copolymers.

ARGET ATRP method (*Activators Regenerated by Electron Transfer Atom Transfer Radical Polymerisation*) is known which is a modification of the ATRP method and allows to control polymerisation with a small (several ppm) concentration of a catalytic complex. Due to this, the obtained homopolymers and copolymers do not require a laborious procedure of purification from the used catalytic materials [*Chem. Rev.* 101 (2001) 2921].

It is known to use ATRP polymerisation in synthesis of PNIPAM polymer using methyl 2-chloropropionate or fluorescein 2-bromoisobutyrate as the polymerisation initiator, and Cu(I)X/L catalytic complexes containing copper(I) halogen salts and ligands L such as tri[(2-dimethylamino)ethyl]amine (Me₆TREN) and 1,1,4,7,7-pentamethyldiethylenetriamine (PMDETA), where the reaction is usually carried out in isopropanol, n-propanol, methanol, ethanol, dimethylformamide (DMF), DMF mixture with water or a mixture of dimethyl sulfoxide and water [*Macrom. Rapid Comm.* 25 (2004) 559; *Polymer Bulletin* 59 (2007) 195; *Macromolecules* 38 (2005) 5937]. The narrowest molecular weight distributions and the highest monomer conversion degrees are obtained using isopropanol as a solvent, Me₆TREN as a complexing ligand and methyl 2-chloropropionate as an initiator [*Macromolecules*, 38 (2005) 5937]. Unfortunately, the use of methyl 2-chloropropionate as the initiator of ATRP does not allow any further modification of the resulting polymer chain due to the inability to modify the terminal group enabling the construction of a second block in the same molecule, which would be composed of a monomer with less activity in ATRP than the NIPAM, *e.g.* styrene.

Choosing the right ATRP initiator is crucial for achieving satisfying results. In contrast to the classical radical polymerisation, R-X initiator is not only a source of an initiating radical R[•] (alkyl or alkylaromatic), but also of a terminal group terminating the polymer chain—the radical X[•] (usually a chlorine or bromine, less often iodine atom) [*Prog. Polym. Sci.* 38 (2013) 63]. The terminal atom (X) should be quickly and selectively transferred between the active (growing) and inactive (dormant) form of the polymer chain, according to the following scheme:



where Cu(I)X/L is a catalytic complex, M is a monomer, P is a polymer.

ARGET ATRP method is based on a constant regeneration of the Cu(I)X/L catalytic complex by a reducing agent, the amount of which significantly exceeds the amount of initiator in the reaction medium. The use of reducer in excess allows the concentration of the catalytic complex to be reduced, it also enables polymerisation in the presence of small amounts of oxygen, so that oxygen does not have to be removed entirely from the polymerisation system. Besides, the obtained copolymers do not require a purification from the catalytic materials used (the content of the catalytic complex in the copolymer is usually at the level of several ppm), which significantly simplifies the synthesis [Langmuir 23 (2007) 4528].

It is known to use chlorinated esters of propionic acid as ATRP initiators for active monomers such as NIPAM. This allows achieving a sufficient process speed to obtain monomer conversion degree at room temperature higher than 70% for several hours while maintaining reasonable control of polymer chain length and its polydispersity degree. In the case of bromine derivative use, the reaction rate is too high, which results in uncontrolled polymer chain termination, and a polydisperse material. In turn, in case of less active monomers, such as styrene, initiation of ATRP with chlorine derivatives is ineffective or does not occur [Macromolecules 45 (2012) 4015]. The reason is probably much higher bond energy between the chlorine atom and the styrene-terminated polymer chain than the bond energy between the chlorine atom and the NIPAM-terminated polymer chain. The catalyst system is not able to transfer the chlorine atom and form an active polymer form capable of propagation. Therefore, to initiate ATRP of less active monomers, such as styrene, it is necessary to use more active bromine derivatives instead of chlorine derivatives.

A method for obtaining PNIPAM-*block*-PS block copolymers using RAFT polymerisation is known, in which both blocks are connected directly (without a molecular linker) [Macromol. Rapid Commun. 33 (2012) 534; J. Polym. Sci.: Part A: Polym. Chem., 46 (2008) 5093]. Also known are methods for obtaining PS-*block*-PNIPAM copolymers in which both blocks are connected in reverse order using RAFT polymerisation [Polymer, 45 (2004) 3643; Colloid. Polym. Sci., 286 (2008) 1079; Macromolecules, 38 (2005) 909]. Polymers obtained using the RAFT method are composed of molecules terminated with the dithiocarboxylate moiety S-C(Z)S- , which may cause their lack of biocompatibility, due to which biomedical applications of such materials may be very limited.

A method of synthesis of PNIPAM-*block*-PS copolymer on a silicon substrate using ATRP is known [Langmuir, 26 (2010) 8582]. Modification of the silicon surface makes it biocompatible, *i.a.* well compatible with blood, and renders properties of an excellent substrate for cell culture [Langmuir, 26 (2010) 8582]. This method assumes construction of the PS block on the previously

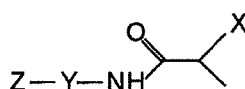
obtained PNIPAM block anchored on the silicon surface. This involves the need of bromine initiator application in the whole process so that it is possible to construct the PS block on the PNIPAM block. Unfortunately, this reduces the control over PNIPAM block polymerisation and results in a PNIPAM-*block*-PS copolymer having high polydispersity index and contaminated with

5 PNIPAM chains, which were terminated with no control in the first stage of the synthesis.

There is an unmet need to develop a polymerisation method that would allow easy, fast and controllable synthesis of block copolymers, BLOCK1-*block*-BLOCK2, *e.g.* PNIPAM-*block*-PS, with low polydispersity index, high purity and good definition of the structure of each block.

10 Summary of the invention

An initiator of ATRP radical polymerisation having a functional group with a substituent active in polymerisation process, is characterised in that it is a bifunctional initiator of a formula



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Y = -R

X = -Cl, -Br, -I

Z = -OH, -NH₂, -NHP, -COOH, -N₃, NCS, NCO

P – protecting group, R – alkyl, aryl or alkylaryl group

it contains at least two functional groups separated by a hydrocarbon moiety Y, where the first

20 functional group has an active substituent X and the second functional group has a protecting group Z, which can be chemically modified with the same or a different substituent than the active substituent X present in the first functional group. According to the invention, the active substituent X is active in ATRP polymerisation process, preferably a halogen substituent, most preferably a chlorine, bromine or iodine substituent. The protecting substituent Z is inactive in

25 ATRP polymerisation process, but it is possible to be substituted with other functional groups, preferably -OH, -NH₂, -NHP, -COOH, -N₃, -NCS, -NCO. The hydrocarbon moiety Z contains an amide group and a hydrocarbon chain R. Initiator according to the invention belongs to the group of organic compounds including functionalised amides of aliphatic and aromatic carboxylic acids, preferably 2-chloro-N-(2-hydroxyethyl)propionamide (NCPAE),

30 N-(2-aminoethyl)-2-chloropropionamide, N-(2-aminoethyl)-2-bromopropionamide or 2-bromo-N-(2-hydroxyethyl)propionamide.

A method of synthesis of 2-chloro-N-(2-hydroxyethyl)propionamide initiator, NCPAE, is characterised in that ethanolamine is subjected to an acylation reaction with 2-chloropropionyl chloride in presence of triethylamine (TEA), wherein the reaction is carried

out under inert atmosphere at room temperature, and the desired compound is obtained with a yield of *ca.* 90%. According to the invention, under inert atmosphere, to the mixture of ethanolamine and triethylamine in methylene chloride, preferably with an excess of ethanolamine, kept at a temperature of 0–15°C, preferably 0°C, under constant stirring, a solution of chloride 2-chloropropionyl in methylene chloride is added drop wise, preferably maintaining a significant excess of ethanolamine in relation to 2-chloropropionyl chloride, and then the reaction is carried out at room temperature for 15–24 h, preferably 19 h, the obtained product is isolated by column chromatography and subjected to recrystallisation.

A method of synthesis of block copolymers using a radical polymerisation initiator having a functional group with a substituent active in polymerisation process, is characterised in that a bifunctional radical polymerisation initiator as defined above is used, wherein:

- a mixture of reagents including bifunctional initiator, catalyst system, solvent and monomer of the first block is loaded into the reactor, air is removed, *e.g.* by using an inert gas flow, an inert gas is introduced (nitrogen or argon), the process temperature is set, and then the radical polymerisation reaction of the first block is initiated,
- polymerisation is carried out leading to formation of the first block, wherein the polymerisation duration is selected depending on the planned length of this chain,
- polymerisation of the first block is stopped,
- the active substituent X of the first functional group is deactivated, preferably by its substitution with a hydrogen atom,
- the second functional group of the bifunctional initiator is activated by substituting the protecting substituent Z with a functional group having the active substituent X,
- product obtained as a result of modification of the product of the first block polymerisation is separated and loaded into a reactor together with a catalyst system, the second block monomer and a solvent, air is removed, *e.g.* by using an inert gas flow, the process temperature is set, and then the radical polymerisation reaction of the second block is initiated,
- second block polymerisation is carried out, wherein the polymerisation time is selected depending on the planned length of this chain,
- polymerisation of the second block is stopped,
- the product of polymerisation, *i.e.* block copolymer BLOCK1-*block*-BLOCK2, is separated.

According to the invention, polymerisation of PNIPAM block is carried out first, followed by polymerisation of PS block, wherein:

- PNIPAM block formation is carried out using NIPAM as a monomer, a bifunctional initiator with an active chloride group, preferably NCPAE, and the reaction is carried out in isopropanol using CuCl/Me₆TREN as a catalyst system, preferably at room temperature, wherein polymerisation time may vary between a few up to several hours depending on the planned length of the first chain,
 - polymerisation of the PNIPAM block is stopped by introducing air into the reaction system,
 - polymers obtained this way are subjected to dehalogenation followed by esterification using α -bromoisobutyryl bromide and triethylamine in anhydrous THF,
 - the inactive functional group of the initiator connected to the PNIPAM block is substituted with bromine to form PNIPAM-Br macroinitiator,
 - PS block formation is carried out using styrene as a monomer, PNIPAM-Br macroinitiator, CuCl₂/PMDETA as a catalyst system, Sn(EH)₂ as a reducing agent, wherein styrene polymerisation is carried out in DMF at an elevated temperature, preferably 90°C, with polymerisation time may vary between a few up to several hours depending on the planned length of the first chain.
 - polymerisation of PS block is stopped by cooling the reaction system to room temperature,
 - the product of polymerisation, *i.e.* block copolymer PNIPAM-*block*-PS, is separated.
- According to the invention, polymerisation of the PS block is carried out first, followed by polymerisation of the PNIPAM block, wherein:
- PS block formation is carried out using styrene as a monomer, a bifunctional initiator with an active bromide group, wherein polymerisation reaction is carried out in DMF, using CuBr₂/PMDETA as a catalyst system, at an elevated temperature, preferably 90°C.
 - PS block formation is stopped by cooling the polymerisation mixture to room temperature,
 - polymers obtained are dehalogenated and then esterified using α -chloroisobutyryl chloride and triethylamine in anhydrous THF,
 - the inactive functional group of the initiator connected to PS block is substituted with chlorine to form the PS-Cl macroinitiator,
 - PNIPAM block formation is carried out using NIPAM as a monomer, PS-Cl macroinitiator, CuCl/Me₆TREN as a catalyst system, Sn(EH)₂ as a reducing agent, and NIPAM polymerisation is carried out in DMF at room temperature, wherein polymerisation time may vary between a few up to several hours depending on the planned length of the chain .
 - polymerisation of the PNIPAM block is stopped by introducing air into the polymerisation mixture,
 - the product of polymerisation, *i.e.* block copolymer PS-*block*-PNIPAM, is separated.

An initiator of ATRP radical polymerisation, a method of its synthesis, and a method of synthesis of low-dispersion polymer and copolymer using this initiator have been described in detail in the examples below, with reference to the attached drawing, in which:

- Fig. 1 General structure of a bifunctional polymerisation reaction initiator;
- 5 Fig. 2 NCPAE initiator synthesis diagram;
- Fig. 3 Diagram of the four-step PNIPAM-*block*-PS block copolymer synthesis using the NCPAE initiator, wherein the subsequent steps provide:
- I. NIPAM polymerisation by ATRP method using the NCPAE initiator,
 - II. Dehalogenation of the resulting polymer by chlorine atoms removal,
 - 10 III. Modification of this polymer by terminal bromine atom introduction,
 - IV. Styrene polymerisation by ARGET ATRP method with the PNIPAM-Br macroinitiator;
- Fig. 4 ^1H NMR spectrum of an exemplary PNIPAM-*block*-PS copolymer sample (PNIPAM-b-PS1 sample, Table 2);
- Fig. 5 Photograph of an exemplary PNIPAM-*block*-PS copolymer sample dissolved in water
15 (PNIPAM-b-PS1 sample, Table 2);
- Fig. 6 ^1H NMR spectrum of an exemplary PNIPAM polymer sample (sample PNIPAM1, Table 1);
- Fig. 7 DSC curve obtained for an exemplary PNIPAM homopolymer sample dissolved in water (PNIPAM1 sample, Table 1, concentration 1.5%);
- 20 Fig. 8 Particle size distribution (by number) in the aqueous solution of the PNIPAM homopolymer sample at 25°C and 45°C (PNIPAM1 sample, Table 1, concentration 1.5%);
- Fig. 9 Molecular weight distributions for PNIPAM polymers obtained, SEC analysis (PNIPAM1, PNIPAM2 and PNIPAM3 samples, Table 1);
- Fig. 10 DSC curve of an exemplary solid-phase PNIPAM-*block*-PS copolymer sample
25 (PNIPAMPS1 sample);
- Fig. 11 DSC curve of an exemplary PNIPAM-*block*-PS copolymer sample in an aqueous solution (PNIPAMPS1 sample);
- Fig. 12 Particle size distributions in aqueous solution, determined by the DLS method, for exemplary PNIPAM-*block*-PS copolymer samples at 25°C and 45°C (PNIPAM-b-PS1
30 sample).

Detailed description of the invention

Subject of this invention is a bifunctional polymerisation initiator containing a halogen active group and a second active group, allowing subsequent polymerisation of various types of
35 polymer blocks, and a synthetic path leading to block copolymers, which consists of 4 steps:

- I. *Polymerisation leading to BLOCK 1 by a method using bifunctional initiator*
- II. *Modification of the polymer obtained in step I - deactivation of 1st active terminal group*
- III. *Modification of the polymer obtained in step II - activation of the 2nd active terminal group*
- IV. *Polymerisation resulting in BLOCK 2 using a macroinitiator obtained in step II*

5 The invention constitutes a solution to the synthetic problem related to the low yield of initiation and propagation of the (co)polymer chain growth at its end, consisting in the use of a bifunctional initiator enabling an independent growth of two polymer blocks at the two initiator poles, wherein these growths are accomplished in two subsequent processes.

10 The invention provides a bifunctional initiator having two terminal moieties: one halogen and the other one, which could be activated in a suitable process. The halogen moiety is the initiator of the first polymerization reaction during which the group, *e.g.* -OH, -NH₂, -NHP, -COOH, -N₃, -NCS, -NCO group, preferably the hydroxyl group, remains inactive. After completion of the first block polymerisation and deactivation of the terminal halogen group, it is possible to easily modify the group and substitute it with a moiety containing another terminal

15 halogen substituent which is the second polymerisation reaction initiator. An exemplary bifunctional initiator is 2-chloro-N-(2-hydroxyethyl)propionamide (NCPAE), a molecule having a chlorine and hydroxyl substituents on opposite poles of the molecule. Other examples of this type of initiators may be N-(2-aminoethyl)-2-chloropropionamide, N-(2-aminoethyl)-2-bromopropionamide, 2-bromo-N-(2-hydroxyethyl)propionamide and others with the general

20 structure depicted in Fig. 1.

 The use of a bifunctional initiator allows polymerisation of one block and constructing it on the halogen pole, while the protecting substituent Z remains inactive. After completion of the first block polymerisation, it is possible to deactivate the halogen moiety and further activate of the hydroxyl moiety to construct the second polymer block at the second pole of the initiator.

25 This allows block polymerisation of polymers of different activities and properties, and the resulting blocks can have different planned lengths/molecular weights. In this way, well-defined polymers and block copolymers with low polydispersity coefficient and a general formula of BLOCK1-*block*-BLOCK2 can be obtained, whereby these blocks can be built of different polymers, and they are connected by a molecular linker constituting the core of a bifunctional initiator.

30 An exemplary block copolymer that can be obtained is PNIPAM-*block*-PS. Such copolymer is amphiphilic, biocompatible and shows thermosensitivity. It is also possible to obtain other block copolymers, for example, copolymers made of a block of polyacrylic acid (PAA)/polymethyl methacrylate (PMM)/ polyacrylonitrile (PAN) and a block of poly-4-methylstyrene (P4MeS)/poly-4-tert-butylstyrene (P4-TbS)/poly-3-methylstyrene (P3MeS) in

35 various combinations and sequences. The following are some exemplary block copolymers

which can be obtained using the initiator of the invention: PAA-*block*-P4MeS; PMM-*block*-P4MeS; PAN-*block*-P4MeS; PAA-*block*-P4TbS; PS-*block*-PNIPAM; PS-*block*-PAA; PAA-*block*-P3MeS.

The bifunctional polymerisation initiator, according to the invention, can also be used to
5 synthesise homopolymers composed of monomers of one type. An initiator having the appropriate active group for one type of polymerisation is then used.

It is also possible to stop the polymerisation process and resume it again, if the active functional group has not been deactivated before.

The polymer materials obtained can find a variety of applications, *e.g.* medical, as
10 carriers for controlled drug release, base materials in tissue engineering, new carriers in gene therapies, and as materials for "intelligent membrane" construction.

NCPAE – bifunctional initiator of polymerisation

A method for obtaining NCPAE by transesterification is known, carried out with isobutyl
15 (S)-2-chloropropionate in ethanol and 1,4-dioxane at elevated temperature [*Monatshefte fuer Chemie*, 119 (1988) 839]. Due to the reversibility of the transesterification reaction and the possibility of ester formation as a by-product, this method does not provide high yields, requires a long reaction time to obtain satisfactory yields (80% yield after 72 h of heating at 60–70°C), which means that the cost of obtaining the right product is high.

20 The synthesis of the 2-chloro-N-(2-hydroxyethyl)propionamide (NCPAE) initiator, according to the invention, is based on the acylation reaction of ethanolamine with 2-chloropropionyl chloride in the presence of triethylamine (TEA). NCPAE is a commercially available compound, but its price is high (around USD 250/1 g), and its availability is limited (quantities offered by sellers: 1 mg, 10 mg, maximum 5 g).

25 NCPAE synthesis, being the subject of the present invention, is carried out at room temperature, using cheap reactants, and leads to the product with a very high yield (90%).

The bifunctional polymerisation initiator NCPAE is an amide derivative of propionic acid containing two "poles" in the molecule: a chlorine atom and a hydroxyl group. Due to the presence of a chlorine atom in the molecule, NCPAE is able to initiate the polymerisation process
30 using ATRP method, while the hydroxyl group remains inactive during polymerisation. After completion of the first block polymerisation, the terminal chlorine group is deactivated, and the inactive hydroxyl group is activated, which can react with carboxylic acids, their anhydrides, and acid halides, which allows easy modification of the polymer chain after the first polymerisation is completed and enables the construction of the second block at the second "pole" of the
35 initiator. Such modification is possible *i.a.* using α -bromoisobutyryl bromide, which allows

introduction of a moiety with the terminal bromine atom into the molecule already containing the first polymer block, and such a macroinitiator is able to initiate the polymerisation of a second polymer block composed of a less reactive monomer than the first one.

The dehalogenation process, *i.e.* the deactivation of the active functional group, is done by transferring the halogen atom to ATRP catalyst system (PMDETA/CuBr) in the presence of tributyltin hydride according to a known procedure [*Macromol. Rapid Commun.* 20 (1999) 66].

The activation process of the protected functional group is done depending on the protective group used and the planned modification. For example, in case of substitution of a hydroxyl group with a bromide substituent, an esterification reaction is carried out using α -bromoisobutyryl bromide and triethylamine in anhydrous THF in a molar ratio of polymer, bromide and triethylamine of 1/1.8/1.3. In turn, in case of hydroxyl group substitution with a chloride substituent, an esterification reaction is carried out using α -chloroisobutyryl chloride and triethylamine in anhydrous THF in a molar ratio of polymer, bromide and triethylamine of 1/1.8/1.3.

Other bifunctional polymerisation initiators

There is an infinite number of bifunctional polymerisation initiators that could be obtained and used in the synthesis of block polymers by the method of the invention. The bifunctional initiator must have two independent functional groups (Fig. 1), of which one active group (*e.g.* chlorine, bromine, iodine, fluorine) is used for the first block polymerisation, while the second group (*e.g.* hydroxyl, amino, carboxyl, azide, cyanate, thiocyanate) remains inactive in the polymerisation reaction. After completion of the first block polymerisation, the terminal active function group is deactivated (*e.g.* halogen is substituted with hydrogen), the second "pole" of the initiator is activated (*e.g.* substitution with chlorine, bromine or iodine) in order to obtain the possibility to initiate the reaction of second block formation in the subsequent polymerisation.

Among the known chemical compounds, function of a bifunctional polymerisation initiator can have, *e.g.* N-(2-aminoethyl)-2-chloropropionamide, N-(2-aminoethyl)-2-bromopropionamide, 2-bromo-N-(2-hydroxyethyl)propionamide. It is also possible to design new chemical compounds that could be used as bifunctional initiators of polymerisation reaction, for example: functionalised amides of aliphatic and aromatic carboxylic acids.

Method of synthesis of NCPAE bifunctional initiator

The initiator synthesis is carried out by means of an acylation reaction using ethanolamine (EA) as a substrate, 2-chloropropionyl chloride (CCP) as an acylating agent, in the

presence of triethylamine (TEA). TEA binds hydrogen chloride formed as a result of the reaction, forming salt (triethylamine hydrochloride), which is easily separated by filtration. The reaction is then carried out in a molar excess of ethanolamine to CCP (*e.g.* in a 4.1/1 molar ratio) so as to prevent double acylation of this compound (via amino and hydroxyl groups). A slight molar excess of TEA to CCP (*e.g.* 1.4/1 molar ratio) is also used, thus ensuring the complete binding of the hydrogen chloride formed as a result of the reaction. The reaction is carried out in a suitably selected solvent, for example, in dichloromethane (DCM) solution, under an inert atmosphere, argon, for example. During the addition of CCP to EA in DCM solution, the mixture is stirred vigorously, and the mixture is cooled (its temperature should be around 0°C) because slowing of the reaction increases its selectivity (the amount of product which is mono-substituted derivative increases). After the addition of reagents, the reaction mixture is left at room temperature, and stirring is continued for another 15-24 h, preferably 19 h. After this time, the proper product is separated from the post-reaction mixture, *e.g.* by column chromatography. Additional product purification is obtained by crystallisation, for example from a 1/1 ethyl acetate/hexane mixture.

Method of low-dispersion block copolymer synthesis

Polymerisation of each block of the desired block copolymer is carried out separately, by subsequently using each of the polymerisation initiator "poles". In this way, it is possible to use optimal chemical (terminal active group, *e.g.* chloride, bromide or iodide) and physical (temperature, pressure, solvent, etc.) conditions for the polymerisation of each block. This enhances process control, which helps to avoid the uncontrolled premature termination of the polymer chains and produces a material with a low polydispersity index and properly selected chain length.

BLOCK1-*block*-BLOCK2 block copolymer synthesis consists of 4 steps:

- I. *Polymerisation leading to BLOCK 1 formation by a method using a bifunctional initiator*
- II. *Modification of the polymer obtained in step I – deactivation of the 1st terminal active group*
- III. *Modification of the polymer obtained in step II – activation of the 2nd active terminal group*
- IV. *Polymerisation resulting in BLOCK 2 formation using a macroinitiator obtained as a result of step III*

Step I and IV are steps of BLOCK1 and BLOCK2 formation respectively, while steps II and III are modifications of the initiator "poles" which allow changing the direction of polymerisation. By separating the polymerisation blocks from each other, precise process control is possible. BLOCK1 and BLOCK2 formation can be stopped at any time, which allows obtaining polymer

chains of a specified length, provided that the relationship between chain length and polymerisation time has been determined experimentally in the determined process conditions.

The method according to the invention could be used with many different block copolymers, for example, copolymers composed of a polyacrylic acid (PAA)/polymethyl methacrylate (PMM)/polyacrylonitrile (PAN) block and a poly-4-methylstyrene (P4MeS)/poly-4-tertbutylstyrene (P4-TbS)/poly-3-methylstyrene (P3MeS) block in various combinations and sequences. Below are some exemplary block copolymers that can be obtained using the bifunctional initiator of the present invention: PAA-*block*-P4MeS; PMM-*block*-P4MeS; PAN-*block*-P4MeS; PAA-*block*-P4TbS; PS-*block*-PNIPAM; PS-*block*-PAA; PAA-*block*-P3MeS.

The bifunctional polymerisation initiator according to the invention can also be used to synthesise homopolymers composed of monomers of one type. An initiator having the appropriate active group for one type of polymerisation is then used.

The method according to the invention allows subsequent block polymerisations to be carried out in any order while maintaining the appropriate polymerisation conditions for each block. It is also possible to stop the polymerisation process and resume it again, provided that the active functional group has not been deactivated before.

Particularly preferred is to use the method of the invention for synthesis of block copolymers with the sequence of PNIPAM-*block*-PS because the obtained copolymers have properties that allow their full potential to be utilised: thermosensitivity, amphiphilicity and biocompatibility due to the possibility of precise chain length control in both blocks, as well as the use of functional groups that do not affect its biocompatibility.

The formation of subsequent polymer blocks and homopolymers using the bifunctional initiator according to the invention is carried out under conditions suitably selected for the nature of the material being synthesised. For example, PNIPAM block formation is carried out using NIPAM as a monomer, an initiator with an active chloride group, in isopropanol using CuCl/Me₆TREN as a catalyst system, at room temperature, where the polymerisation time is from a few up to several hours depending on the planned length of the first chain. In turn, PS block formation is carried out using styrene as a monomer, an initiator with an active bromide group, CuCl₂/PMDETA as a catalyst system, Sn(EH)₂ as a reducing agent, and the styrene polymerisation is carried out in DMF at a styrene/DMF volume ratio of 1/1, at 80–100°C, preferably 90°C, using molar ratios of PNIPAM reagents to styrene, copper(II) halide, ligand and Sn(EH)₂ of 1/400/0.006/0.1/0.1, where the polymerisation time is from a few up to several hours depending on the planned length of the first chain.

The copolymers obtained by the method of the invention, with the appropriate selection of polymer blocks, may have amphiphilic and thermosensitive properties, due to which they can

have a variety of medical applications as carriers for controlled drug release, base materials in tissue engineering, new carriers in gene therapies, but also as materials for "smart membrane" construction.

The solution according to the invention is presented below in embodiments which do not limit its scope or application.

Example 1. NCPAE SYNTHESIS:

2.5 mL of ethanolamine (41 mmol), 2 mL of triethylamine (14 mmol) and 80 mL of methylene chloride were placed in a pre-degassed (under nitrogen flow) 250 mL flask. The flask placed on a magnetic stirrer was cooled in water/ice bath. The mixture was flushed with nitrogen for another 15 minutes. Then a solution containing 1 mL of 2-chloropropionyl chloride (10 mmol) dissolved in 20 mL of methylene chloride was added drop wise over 15 minutes. During acid chloride addition, a white precipitate gradually appeared in the flask. When addition was completed, the reaction was carried out for 19 hours at room temperature. The product was isolated by column chromatography (silica gel packing, chloroform/methanol 95:5 mixture was used as eluent). Separation was monitored by thin layer chromatography (TLC). Solvent contained in the product fractions was evaporated using a rotary evaporator. The product was crystallised from a mixture of ethyl acetate and hexane in a volume ratio of 1:1. 1.4 g of product was obtained. The reaction yield was 90%.

The molecular structure of 2-chloro-N-(2-hydroxyethyl)propionamide, NCPAE, ($C_5H_{10}ClNO_2Na$), has been experimentally confirmed by high-resolution mass spectrometry and nuclear magnetic resonance spectroscopy:

HRMS $[M+H]^+$: predicted $M/Z = 152.0473$, measured $M/Z = 152.0431$

HRMS $[M-H]^-$: predicted $M/Z = 150.0327$, measured $M/Z = 150.0368$

^1H NMR (300 MHz, $CDCl_3$): 7.04 (bs, 1H) $-NH-$; 4.42 (q, $J=7$, 1H) $-CH(Cl)CH_3$; 3.80–3.70 (m, 2H) $-CH_2-OH$; 3.50–3.35 (m, 2H) $-NH-CH_2-$; 2.65 (t, $J=6$, 1H) $-OH$; 1.73 (d, $J=9$, 3H) $-CH_3$;

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 C=O; 61.9 $-CH_2-OH$; 55.9 $-CH(Cl)CH_3$, 42.6 $-NH-CH_2-$, 22.7 $-CH_3$;

Melting point, $T = 67-68^\circ C$.

Example 2. POLYMERISATION LEADING TO PNIPAM BLOCK FORMATION (step I):

Schlenk flask (previously evacuated and filled with argon), was charged with N-isopropylacrylamide (NIPAM), and isopropanol (1:1 mass ratio to monomer) and copper(I) chloride were added, the mixture was degassed under argon flow for 30 minutes, then sonicated for 5 minutes, then transferred to a Schlenk flask placed on a magnetic stirrer (previously

evacuated and filled with purified argon). Then the appropriate volume of tri[2-(dimethylamino)ethyl]amine (Me₆TREN) was added. After Me₆TREN addition, the mixture turned intense green, which indicates the formation of a complex compound with copper ions. The mixture was degassed under argon flow for 30 minutes. Then a (degassed) solution of NCPAE in isopropanol was introduced. Polymerisation was carried out at room temperature, with vigorous stirring on magnetic stirrer.

Polymerisation reactions were carried out which differed in duration, from 2 hours to 22 hours and molar ratio of monomer to initiator, copper(I) chloride and ligand used (Table 1). The polymers were isolated and purified as a result of a procedure consisting of several steps:

- 1) evaporation of isopropanol using a rotary evaporator, 2) dissolution of the resulting precipitate in THF, 3) passing the resulting solution through a column packed with basic alumina, 4) precipitation of polymers from the solution with hexane. The resulting polymers were dried in a vacuum dryer for 24 h at 40°C. NIPAM polymerisation yield was determined by gravimetric method. Average molecular weights and polydispersity indices for the polymers obtained were determined by the SEC method, using DMF with addition of LiBr (1% by weight) as eluent. For all PNIPAM polymers obtained, the determined polydispersity index values are close to one, which indicates a narrow distribution of their molecular weights.

Table 1. Polymerisation times (PNPAM block formation), reagent molar ratios used, yields obtained, experimental and theoretical average molecular weights, and polydispersity indices (PDI) of obtained polymers.

Polymer	Time [h]	[I]/[M]/[CuCl]/[L] ^a	Yield ^b [%]	Experimental weight M _n [Da]	Theoretical weight M _n [Da]	PDI
PNIPAM 1	4	1:50:1:1	40,2	2200 ^c	2270	1.17 ^c
PNIPAM 2	22	1:50:1:1	87,2	4100 ^c	4900	1.14 ^c
PNIPAM 3	2	1:200:1:1	63,8	5900 ^c	14400	1.31 ^c

^a Molar ratio of initiator to monomer, copper(I) chloride and ligand,

^b Gravimetrically determined as the ratio of the mass of polymer obtained to the mass of monomer used

^c Determined based on SEC analysis using DMF with addition of LiBr (1%) as eluent

^d Determined as $Y \times [M]/[I] \times M_w$, where Y is yield, M_w is NIPAM molecular weight

PNIPAM polymers obtained in the first block formation reaction were characterised by ¹H NMR spectroscopy (Fig. 6), differential scanning calorimetry (DSC) (Fig. 7) and dynamic light scattering (DLS) (Fig. 8).

NMR measurements confirmed the assumed molecular structures of the polymers obtained: ¹H NMR (300 MHz, CDCl₃): δ: 4.01 (bs) -CH(CH₃)₂; 2.30–1.25 broad signals -CH₂-CH(R)-; 1.14 (bs) -CH(CH₃)₂;

DSC measurements in aqueous solutions showed an endothermic phase transition of the polymers obtained in a narrow PTT range = 42.8–44.0°C with peak minimum at 43°C (PNIPAM1, Table 1). A narrow phase transition temperature range indicates a narrow molecular weight distribution in the test sample. For the remaining polymers obtained, the phase transition occurred at a very similar temperature. Below the PTT, the polymers obtained are water-soluble, but above this temperature they are water-insoluble, as illustrated in the pictures on the graph (Fig. 7).

Solid phase DSC measurements showed a glass transition temperature of $T_g = 119.6^\circ\text{C}$ for the PNIPAM1 homopolymer (Fig. 12). DLS measurements were carried out at 25°C and 45°C. Particle size (hydrodynamic diameter) distributions determined by number for PNIPAM1 sample (Table 1) is shown on the graph of Fig. 8. At 25°C (below PTT) PNIPAM is well soluble in water and the recorded average particle size is 4.9 nm, whereas at 45°C, above the LCST of the polymer, when PNIPAM is not water-soluble, aggregates are formed whose average hydrodynamic diameters are 135.9 nm and 1006.0 nm.

The results of DSC and DLS analyses confirm the thermosensitive properties of PNIPAM polymers obtained using the bifunctional initiator according to the invention.

SEC analyses showed that the polymers obtained were characterised by narrow molecular weight distributions. The average molecular weights M_n determined on their basis were in the range 2200–5600 Da (Fig. 9, Table 1). The determined polydispersity index values were close to one (1.14–1.36) and the average molecular weights were close to those predicted theoretically based on the monomer:initiator molar ratio used (Table 1). This makes it possible to conclude that the polymerisation reactions with bifunctional initiator according to the invention were running in a controlled manner.

Example 3. DEACTIVATION OF THE FIRST TERMINAL GROUP (step II):

A 25 mL flask, previously degassed in argon flow, was charged with anhydrous THF, then PNIPAM (1 g PNIPAM/7 mL THF), CuBr and 1,1,4,7,7-pentamethyldiethylenetriamine (PMDETA) were dissolved in it; after adding the latter the solution turned deep green. The mixture was degassed under argon flow for 30 minutes. Then tributyltin hydride was added to the reaction mixture. The molar ratio of PNIPAM to copper(I) bromide, PMDETA ligand and tributyltin hydride was 1:0.5:0.5:3. The reaction was carried out at 60°C for 4 hours, with reaction mixture left on a magnetic stirrer in a thermostatic oil bath. After putting the flask with the reaction mixture into oil bath, a change of colour to light brown was observed, after 20 minutes the mixture turned dark brown. After completing the reaction by flask opening and exposing the reaction

mixture to air, its colour became intense green again. The post-reaction mixture was passed through a column packed with basic alumina, then concentrated using a rotary evaporator. The reaction product was precipitated with hexane, filtered off and dried in a vacuum dryer (24 h, 40°C).

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Example 4. ACTIVATION OF THE SECOND TERMINAL GROUP (step III):

A 250 mL flask was charged with PNIPAM, then anhydrous THF (1 g PNIPAM/40 mL THF) and triethylamine were added by syringe countercurrently to argon flow, and the reaction mixture was degassed under argon flow. A previously prepared and degassed solution of α -bromoisobutyryl bromide in anhydrous THF was then added. The molar ratio of PNIPAM to triethylamine and α -bromoisobutyryl bromide was 1:1.8:1.3. The reaction mixture was left on magnetic stirrer. The reaction was carried out at room temperature for 24 hours, under argon. During the reaction, a small amount of pale yellow precipitate was observed to appear in the flask. The resulting precipitate (triethylamine hydrobromide) was removed from the post-reaction mixture using 0.45 μ m syringe filter. The mixture was then passed through a column packed with basic alumina. The solution obtained after passing through the column was concentrated using a rotary evaporator, and then the polymer was precipitated with hexane and filtered on G3 Schott funnel. The positive result of the esterification reaction was confirmed by elemental analysis. It showed the presence of bromine in the polymer in the range of 1–2.3%.

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Example 5. STYRENE POLYMERISATION – PS BLOCK FORMATION (step IV):

Copolymerisation with styrene by ARGET ATRP method was carried out as follows: a 50 mL flask pre-degassed in argon flow and charged with bromine functionalised PNIPAM, styrene and DMF (volume ratio of DMF to styrene 1:1). The mixture was degassed under argon flow for 20 minutes. A previously prepared solution of copper(II) salt and ligand both dissolved in DMF was then added. The almost colourless mixture was again degassed under argon flow for 10 minutes, after which a previously prepared and degassed solution of tin(II) 2-ethylhexanoate in DMF was added. The molar ratio of PNIPAM to styrene, copper(II) halide, ligand and $\text{Sn}(\text{EH})_2$ was the same for all syntheses 1:400:0.006:0.1:0.1. The reaction was carried out at 90°C or 110°C at various times, from 4 hours to 45.7 hours (Table 2). The reaction mixture was stirred on magnetic stirrer. The copolymer was isolated by evaporation of the solvent followed by dissolution in THF and precipitation with hexane. The white precipitate was filtered on G4 Schott funnel. The filtrate after precipitation with hexane was concentrated using a rotary evaporator, followed by precipitation with methanol. The copolymers obtained directly from

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step IV contained a small fraction of polystyrene, which was removed by washing the precipitate with toluene until the filtrate did not become cloudy when methanol added (until it was polystyrene free).

The use of a catalyst system consisting of copper(II) chloride and Me₆TREN allowed to obtain a copolymer at 110°C in which polystyrene block constituted about 80% of the molecular weight. A high degree of styrene conversion > 50% was obtained. However, the molecular weight distribution in the resulting copolymer turned out to be relatively wide.

When PMDETA is used, the copolymerisation runs slower and in combination with CuCl₂ at 90°C the degrees of monomer conversion are high just after 8 hours of reaction. The average molecular weight determined from SEC analysis indicates that both blocks are of similar length. NMR spectrum analysis leads to similar estimates. Assuming integration of 4.01 ppm chemical shift signal (proton in the PNIPAM isopropyl group) equal to 1, integration of signals derived from protons in the PS aromatic ring (5 protons) and subtracting integration for -NH equal to integration for protons from the isopropyl group allows to estimate that PNIPAM block: PS block = 1:0.7, and for PNPS2 it is 1:1.

Table 2. Conditions for conducting PNIPAM-block-PS copolymer syntheses using the ARGET ATRP method (reaction temperatures, times, catalyst systems used), obtained monomer (styrene) conversion degrees, number average molecular weights of obtained copolymers and polymers used for their synthesis.

Copolymer	Time [h]	Temp. [°C]	Catalyst system	Conversion ^a [%]	PNIPAM M _n [Da] ^b	PNIPAM- <i>b</i> -PS M _n [Da] ^b
PNIPAM- <i>b</i> -PS1	4	90	CuCl ₂ /PMDETA	10	2200	5200
PNIPAM- <i>b</i> -PS2	8	90	CuCl ₂ /PMDETA	28.4	2200	6500
PNIPAM- <i>b</i> -PS3	24	110	CuCl ₂ /Me ₆ TREN	54.8	5600	25400
PNIPAM- <i>b</i> -PS4	46	110	CuCl ₂ /PMDETA	37.5	5600	7500
PNIPAM- <i>b</i> -PS5	48	110	CuBr ₂ /bpy	38.7	4100	15200

^a determined by gas chromatography,

^b determined by SEC chromatography using DMF with addition of LiBr (1%) as eluent

The copolymers obtained were characterised by ¹H NMR spectroscopy, differential calorimetry (DSC) in solid phase (Fig. 10) and aqueous solutions (Fig. 11), and by DLS (Fig. 12). The obtained results confirmed the structure of the obtained copolymers and their thermosensitive properties.

The ¹H NMR spectra for the obtained copolymers confirmed the presence of PNIPAM block and PS block (Fig. 4), the 4.01 ppm chemical shift signal corresponds to the proton in PNIPAM isopropyl group, and broad signals in the range of 6.57–7.26 ppm correspond to protons in aromatic ring in PS block and protons from amide groups.

^1H NMR (300 MHz, CDCl_3) δ : 7.25–6.80, 6.75–6.25 broad signals (bs) NH belonging to PNIPAM block and ArH belonging to the PS block; 4.01 (bs) $\text{CH}(\text{CH}_3)_2$ belonging to PNIPAM block; 2.30–1.25 broad signals belonging to the PNIPAM and PS polymer chain $-\text{CH}_2-\text{CH}(\text{R})-$; 1.14 (bs) $\text{CH}(\text{CH}_3)_2$ belonging to PNIPAM block.

5 DSC measurements in solid phase showed that the copolymer samples consist of two polymer blocks because two bends were observed on the DSC measurement curve. $T_{g1} = 121.3^\circ\text{C}$ corresponds to PNIPAM block, and this value is close to the value obtained for pure PNIPAM, while $T_{g2} = 96.2^\circ\text{C}$ corresponds to PS block.

DSC measurements in aqueous solution allowed determination of phase transition
10 temperature of PNIPAM-*block*-PS1 copolymer in the PTT range = $30.1\text{--}37.5^\circ\text{C}$. As expected, these values are lower than for PNIPAM1 sample. The temperature range in which the phase transition occurs is much wider than for the PNIPAM sample, which is associated with the broader molecular weight distribution of the copolymer in relation to homopolymer used in the second polymerisation step.

15 Using dynamic light scattering (DLS) method aqueous solution of PNIPAM-*block*-PS1 sample was tested at 25°C and 45°C (Fig. 12). At 25°C , below PTT of PNIPAM-*block*-PS copolymer, particles with a mean hydrodynamic diameter of 619.5 nm were recorded. In turn, at 45°C , the average particle size recorded in the sample was 297.4 nm. The reduction in particle size at a temperature higher than the phase transition temperature of the copolymer is associated with
20 the shrinkage of PNIPAM block, and thus reduction in the volume of aggregates formed by the copolymer.

After dissolving the obtained PNIPAM-*block*-PS1 copolymer in water, a foam appeared (Fig 5) and a decrease in the water surface tension was observed, which indicates copolymer's amphiphilic nature resulting from the presence of a hydrophobic and hydrophilic fragment in its
25 particles. As a result, the obtained product can form micelles in water and behave in a similar way to surfactants.

Glossary of abbreviations used:

ATRP – Atom transfer radical polymerisation

SFRP – Stable free radical polymerisation

ARGET ATRP – Activators regenerated by electron transfer atom transfer radical polymerisation

bpy – 2,2'-bipyridine

CCP – 2-chloropropionyl chloride

DCM – Dichloromethane

DMF – N,N-dimethylformamide

EA – Ethanolamine

DLS – Dynamic light scattering

DSC – Differential scanning calorimetry

Me₆TREN – Tri[(2-dimethylamino)ethyl]amine

NCPAE – 2-chloro-N-(2-hydroxyethyl)propionamide

PDI – Polydispersity index

PMDETA – 1,1,4,7,7-pentamethyldiethylenetriamine

PNIPAM – Poly(N-isopropylacrylamide)

PS – Polystyrene

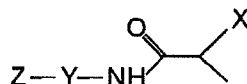
PTT – Phase transition temperature

Sn(EH)₂ – Tin(II) 2-ethylhexanoate

TEA – Triethylamine

Claims

1. An initiator of ATRP radical polymerisation having a functional group with a substituent active in polymerisation process, **characterised in that** it is a bifunctional initiator of a formula



Y = -R

X = -Cl, -Br, -I

Z = -OH, -NH₂, -NHP, -COOH, -N₃, NCS, NCO

P – protecting group, R – alkyl, aryl or alkylaryl group

it contains at least two functional groups separated by a hydrocarbon moiety Y, where the first functional group has an active substituent X and the second functional group has a protecting group Z, which can be chemically modified with the same or a different substituent than the active substituent X present in the first functional group.

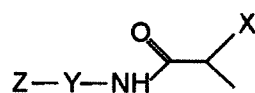
2. Initiator according to claim 1, **characterised in that** the active substituent X is active in ATRP polymerisation process, preferably a halogen substituent, most preferably a chlorine, bromine or iodine substituent.
3. Initiator according to claim 1, **characterised in that** the protecting substituent Z is inactive in ATRP polymerisation process, but it is possible to be substituted with other functional groups, preferably -OH, -NH₂, -NHP, -COOH, -N₃, -NCS, -NCO.
4. Initiator according to claim 1, **characterised in that** the hydrocarbon moiety Z contains an amide group and a hydrocarbon chain R.
5. Initiator according to claim 1, **characterised in that** it belongs to the group of organic compounds including functionalised amides of aliphatic and aromatic carboxylic acids, preferably 2-chloro-N-(2-hydroxyethyl)propionamide (NCPAE), N-(2-aminoethyl)-2-chloropropionamide, N-(2-aminoethyl)-2-bromopropionamide or 2-bromo-N-(2-hydroxyethyl)propionamide.
6. A method of synthesis of 2-chloro-N-(2-hydroxyethyl)propionamide initiator, NCPAE, **characterised in that** ethanolamine is subjected to an acylation reaction with 2-chloropropionyl chloride in presence of triethylamine (TEA), wherein the reaction is carried out under inert atmosphere at room temperature, and the desired compound is obtained with a yield of *ca.* 90%.

7. A method according to claim 6, **characterised in that** under inert atmosphere, to the mixture of ethanolamine and triethylamine in methylene chloride, preferably with an excess of ethanolamine, kept at a temperature of 0–15°C, preferably 0°C, under constant stirring, a solution of chloride 2-chloropropionyl in methylene chloride is added drop wise, preferably maintaining a significant excess of ethanolamine in relation to 2-chloropropionyl chloride, and then the reaction is carried out at room temperature for 15–24 h, preferably 19 h, the obtained product is isolated by column chromatography and subjected to recrystallisation.
8. A method of synthesis of block copolymers using a radical polymerisation initiator having a functional group with a substituent active in polymerisation process, **characterised in that** a bifunctional radical polymerisation initiator as defined in claims 1–5 is used, wherein
 - a mixture of reagents including bifunctional initiator, catalyst system, solvent and monomer of the first block is loaded into the reactor, air is removed, *e.g.* by using an inert gas flow, an inert gas is introduced (nitrogen or argon), the process temperature is set, and then the radical polymerisation reaction of the first block is initiated,
 - polymerisation is carried out leading to formation of the first block, wherein the polymerisation duration is selected depending on the planned length of this chain,
 - polymerisation of the first block is stopped,
 - the active substituent X of the first functional group is deactivated, preferably by its substitution with a hydrogen atom,
 - the second functional group of the bifunctional initiator is activated by substituting the protecting substituent Z with a functional group having the active substituent X,
 - product obtained as a result of modification of the product of the first block polymerisation is separated and loaded into a reactor together with a catalyst system, the second block monomer and a solvent, air is removed, *e.g.* by using an inert gas flow, the process temperature is set, and then the radical polymerisation reaction of the second block is initiated,
 - second block polymerisation is carried out, wherein the polymerisation time is selected depending on the planned length of this chain,
 - polymerisation of the second block is stopped,
 - the product of polymerisation, *i.e.* block copolymer BLOCK1-*block*-BLOCK2, is separated.

9. A method according to claim 8, **characterised in that** polymerisation of P NIPAM block is carried out first, followed by polymerisation of PS block, wherein
- PNIPAM block formation is carried out using NIPAM as a monomer, a bifunctional initiator with an active chloride group, preferably NCPAE, and the reaction is carried out in isopropanol using CuCl/Me₆TREN as a catalyst system, preferably at room temperature, wherein polymerisation time may vary between a few up to several hours depending on the planned length of the first chain,
 - polymerisation of the PNIPAM block is stopped by introducing air into the reaction system,
 - polymers obtained this way are subjected to dehalogenation followed by esterification using α -bromoisobutyryl bromide and triethylamine in anhydrous THF,
 - the inactive functional group of the initiator connected to the PNIPAM block is substituted with bromine to form PNIPAM-Br macroinitiator,
 - PS block formation is carried out using styrene as a monomer, PNIPAM-Br macroinitiator, CuCl₂/PMDETA as a catalyst system, Sn(EH)₂ as a reducing agent, wherein styrene polymerisation is carried out in DMF at an elevated temperature, preferably 90°C, with polymerisation time may vary between a few up to several hours depending on the planned length of the first chain.
 - polymerisation of PS block is stopped by cooling the reaction system to room temperature,
 - the product of polymerisation, *i.e.* block copolymer PNIPAM-*block*-PS, is separated.
10. A method according to claim 9, **characterised in that** polymerisation of the PS block is carried out first, followed by polymerisation of the PNIPAM block, wherein
- PS block formation is carried out using styrene as a monomer, a bifunctional initiator with an active bromide group, wherein polymerisation reaction is carried out in DMF, using CuBr₂/PMDETA as a catalyst system, at an elevated temperature, preferably 90°C.
 - PS block formation is stopped by cooling the polymerisation mixture to room temperature,
 - polymers obtained are dehalogenated and then esterified using α -chloroisobutyryl chloride and triethylamine in anhydrous THF,
 - the inactive functional group of the initiator connected to PS block is substituted with chlorine to form the PS-Cl macroinitiator,

- PNIPAM block formation is carried out using NIPAM as a monomer, PS-Cl macroinitiator, CuCl/Me₆TREN as a catalyst system, Sn(EH)₂ as a reducing agent, and NIPAM polymerisation is carried out in DMF at room temperature, wherein polymerisation time may vary between a few up to several hours depending on the planned length of the chain.
- polymerisation of the PNIPAM block is stopped by introducing air into the polymerisation mixture,
- the product of polymerisation, *i.e.* block copolymer PS-*block*-PNIPAM, is separated.

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Y = -R

X = -Cl, -Br, -I

Z = -OH, -NH₂, -NHP, -COOH, -N₃, NCS, NCO

P – protecting group, R – alkyl, aryl or alkylaryl group

Fig. 1

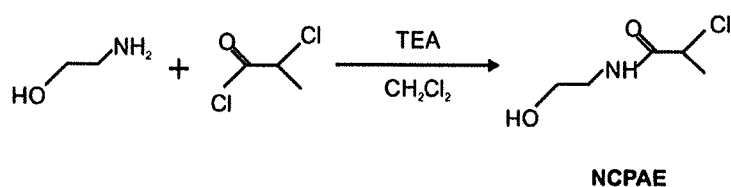
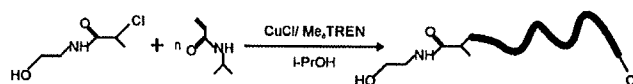
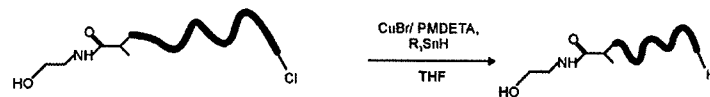


Fig. 2

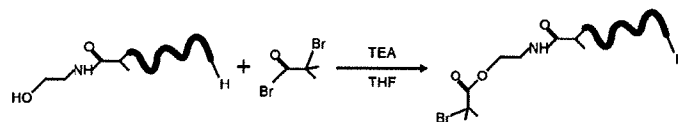
STEP I



STEP II



STEP III



STEP IV

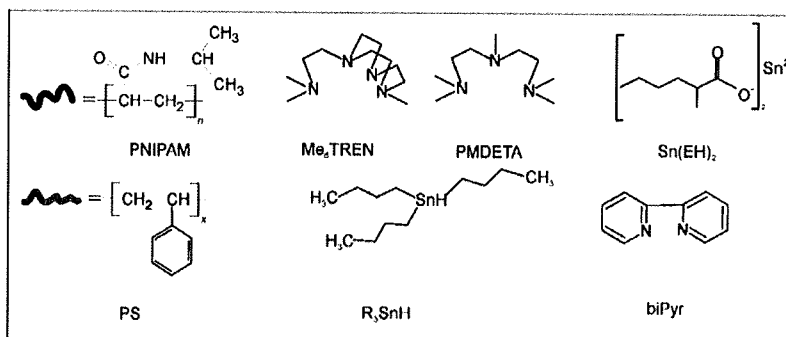
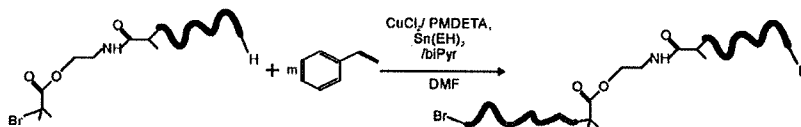


Fig. 3

2/6

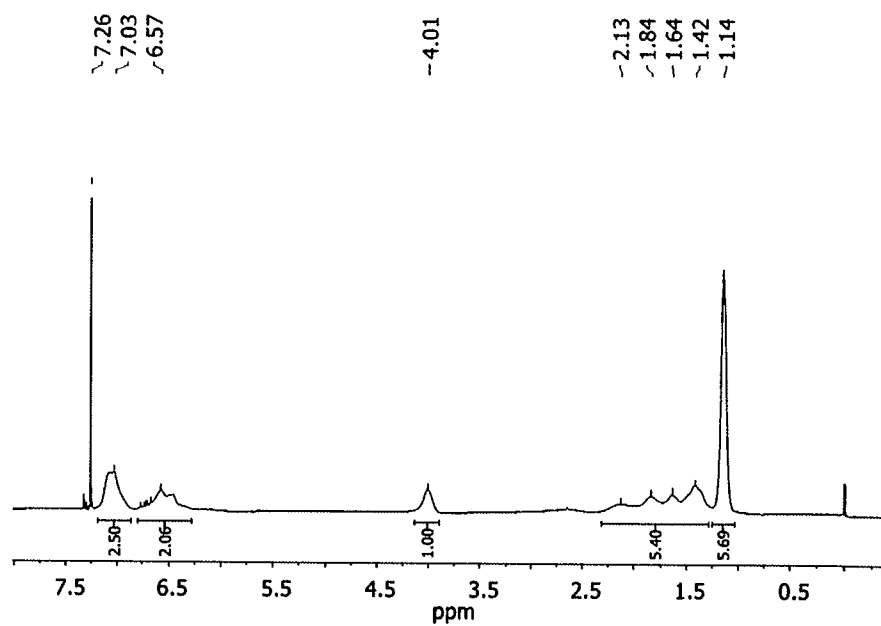


Fig. 4

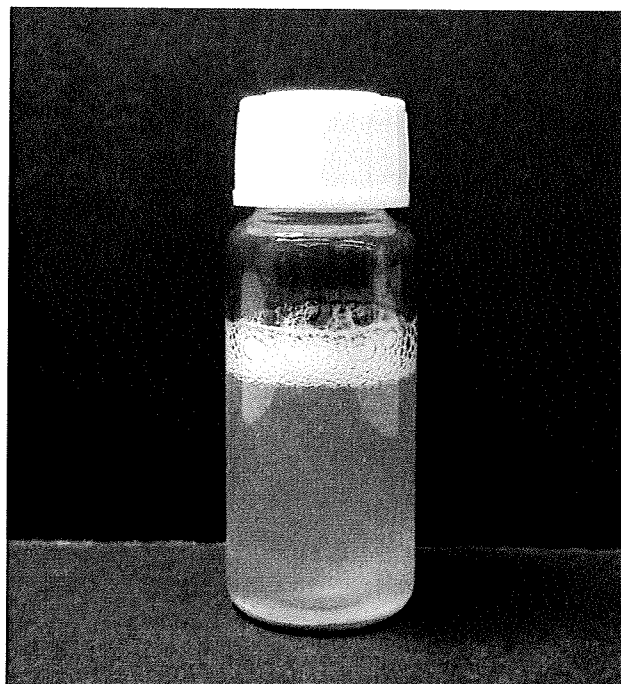


Fig. 5

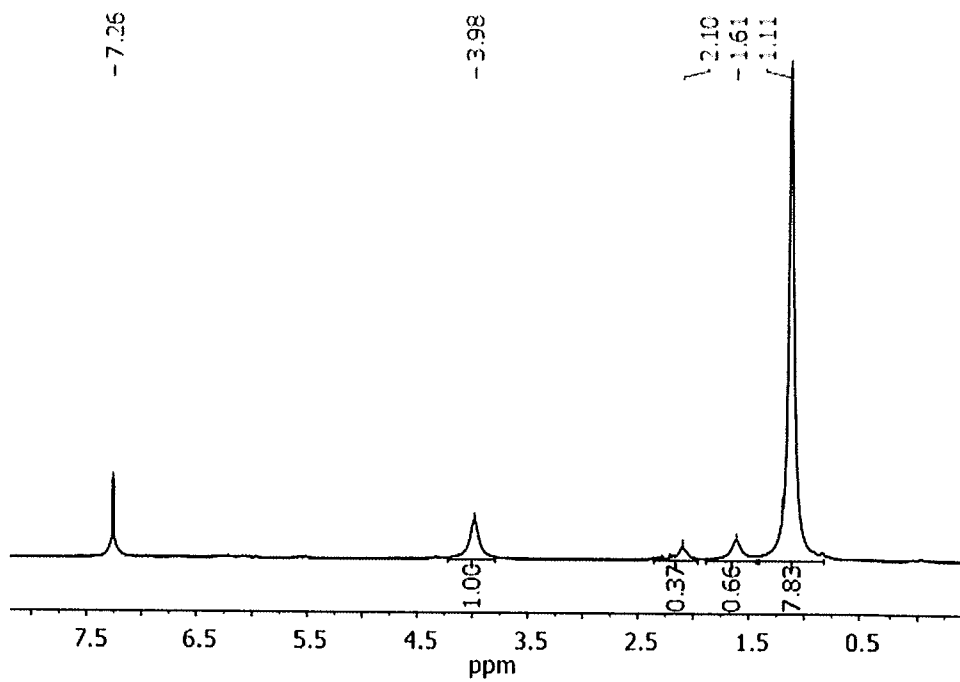


Fig. 6

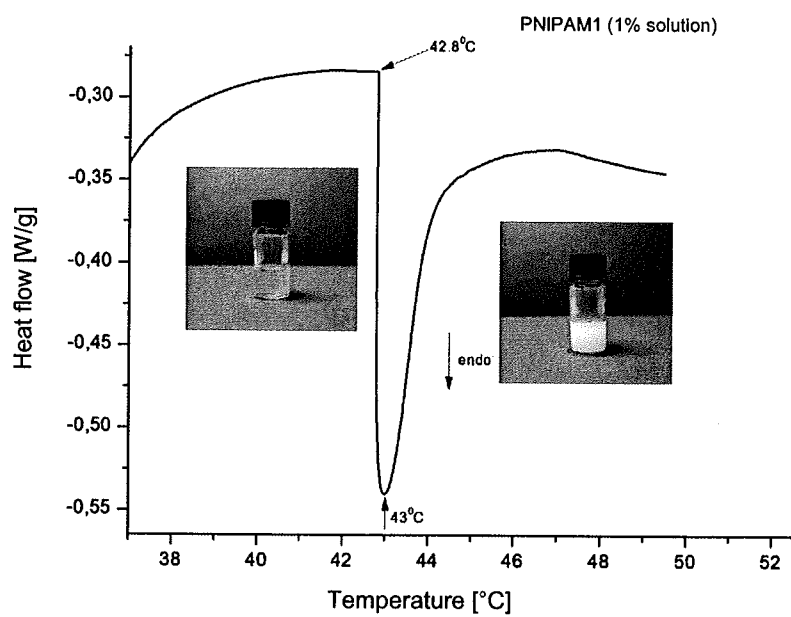


Fig. 7

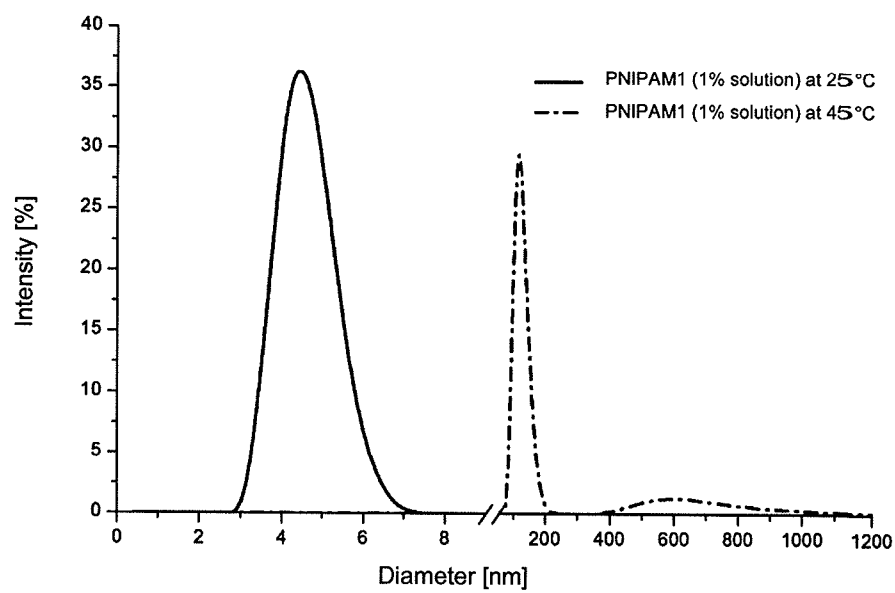


Fig. 8

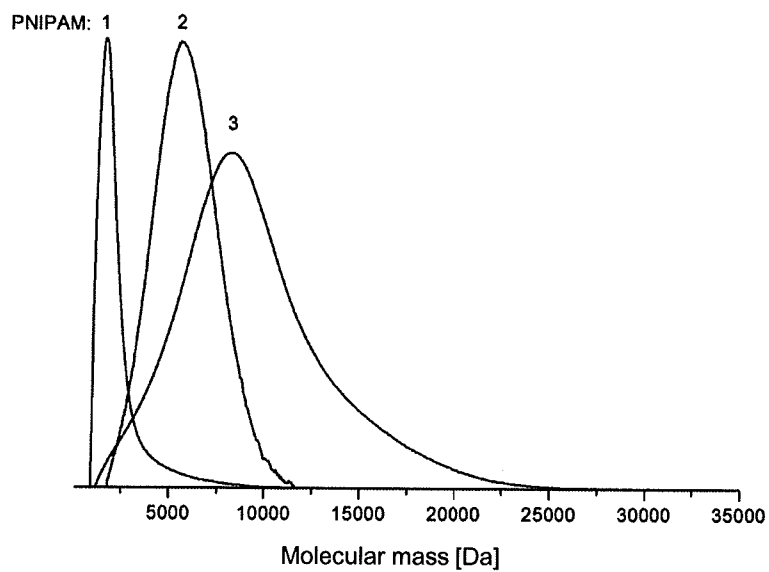


Fig. 9

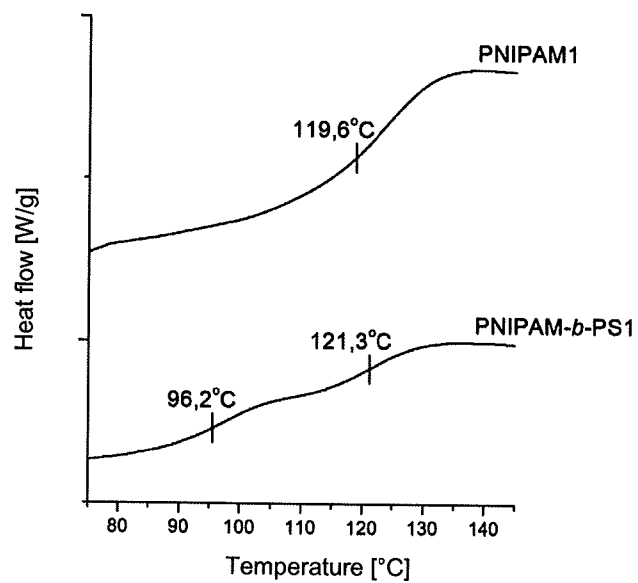


Fig. 10

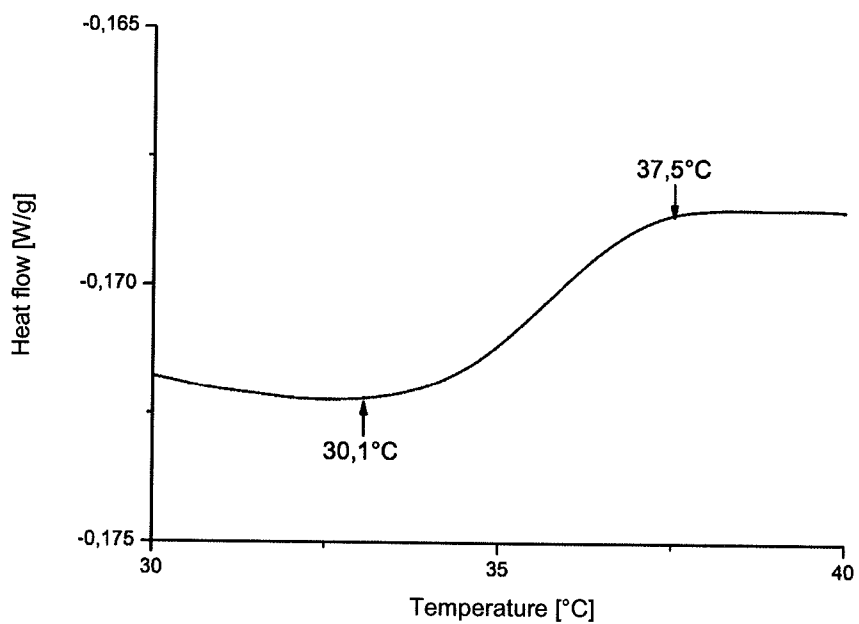
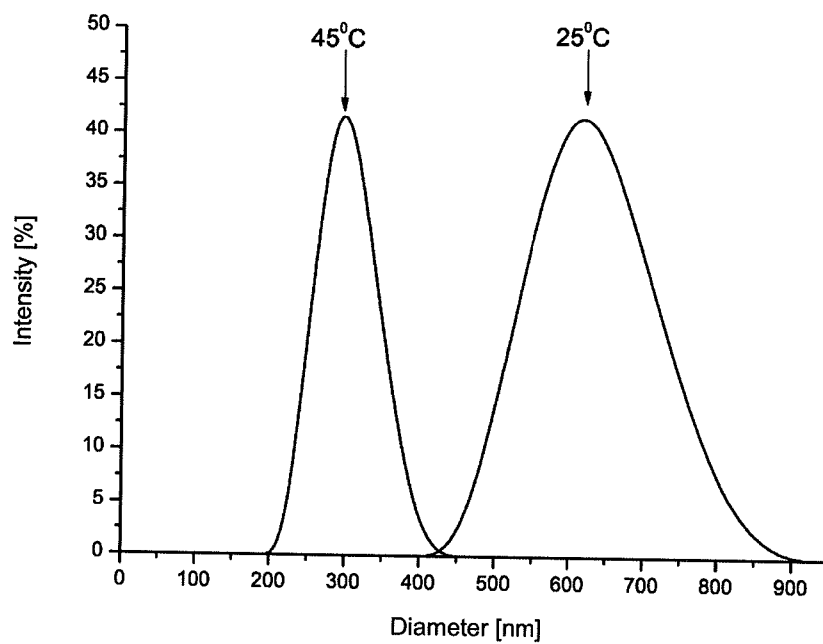


Fig. 11

**Fig. 12**

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2020/000052

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08F293/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 9 June 2016 (2016-06-09), XP002800541, Database accession no. 1928607-04-8 abstract	1-5
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 24 February 2019 (2019-02-24), XP002800542, Database accession no. 2271581-99-6 abstract ----- -/-	1-5



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See patent family annex.

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Date of the actual completion of the international search

30 September 2020

Date of mailing of the international search report

27/10/2020

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Authorized officer

Madalinski, Maciej

INTERNATIONAL SEARCH REPORT

International application No

PCT/PL2020/000052

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 947 527 A1 (GOODRICH CO B F [US]) 6 October 1999 (1999-10-06) example 10	8-10
A	----- example 10	1-7
X	JAN HEGEWALD ET AL: "End-functionalized polystyrene by ATRP: A facile approach to primary amino and carboxylic acid terminal groups", JOURNAL OF POLYMER SCIENCE PART A: POLYMER CHEMISTRY, vol. 47, no. 15, 1 August 2009 (2009-08-01), pages 3845-3859, XP055734914, US ISSN: 0887-624X, DOI: 10.1002/pola.23451 Scheme 2, Scheme 3 -----	1-10
X	WO 2007/083097 A1 (WARWICK EFFECT POLYMERS LTD [GB]; HADDLETON DAVID [GB] ET AL.) 26 July 2007 (2007-07-26) pages 6, 10, 19 and 37; claims 1-23 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/PL2020/000052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0947527	A1	06-10-1999	NONE

WO 2007083097	A1	26-07-2007	US 2007219330 A1 20-09-2007
			WO 2007083097 A1 26-07-2007
