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Articles

Well-Defined (Co)polymers with 5-Vinyltetrazole Units via Combination of Atom Transfer Radical (Co)polymerization of Acrylonitrile and “Click Chemistry”-Type Postpolymerization Modification

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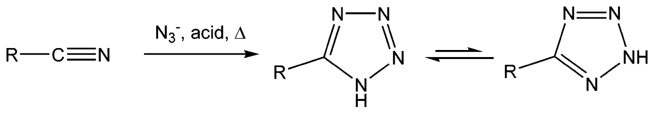
ABSTRACT: Well-defined homo- and copolymers of acrylonitrile were prepared by atom transfer radical polymerization, which were further modified using a “click chemistry” reaction with sodium azide and zinc chloride to yield polymeric materials with 5-vinyltetrazole units. Using optimized reaction conditions ($[NaN_3]:[ZnCl_2]:[RCN] = 4:1:1$ in DMF at 120 °C for 48−50 h), essentially complete transformation of the nitrile groups was achieved, as judged from IR and ^{13}C NMR spectra. The produced tetrazole-containing polymers had markedly better solubility or swellability in protic solvents (methanol or aqueous base solutions) compared to the precursors. Random copolymers of acrylonitrile and styrene were also grown from polystyrene and silica particles with immobilized initiator groups and were similarly modified to the corresponding tetrazole-containing polymers. All materials were characterized by means of thermogravimetry, which showed that the polymeric tetrazoles started to decompose with evolution of significant amounts of gas at 120−190 °C, i.e., at lower (by 60−130 °C) temperature than the starting nitrile-based materials.

Introduction

The tetrazoles RCN_4R' belong to a group of five-membered heterocycles, the azoles. Those with no substituent at any of the nitrogen atoms (RCN_4H) are acidic, with pK_a values similar to carboxylic acids RCO_2H (pK_a(tetrazole) = 4.89, pK_a(5-methyltetrazole) = 5.56, while $pK_a(CH_3CO_2H) = 4.75$[1]) and are thus sometimes referred to as “tetrazolic acids”. Both classes of compounds are thus dissociated at physiological pH. However, tetrazoles and tetrazolate anions are more lipophilic and more stable toward many methabolytic reactions than the carboxylates. These features make them important compounds for the design of drugs such as antibiotics, antiviral, antiallergic, antihypertensive, and radioprotective agents. The first approved drugs for AIDS treatment are, in fact, substituted 3′-tetrazolo-3′-deoxythymidines.[2−4] Tetrazole and its derivatives have found significant application in biomedical sciences, organic synthesis, and coordination chemistry[5,6] and as components of explosives.[3] Tetrazoles are widely used as activators in the coupling reaction between phosphoramidite monomers and immobilized oligonucleotides possessing a free 5′-hydroxy group—an essential step in the synthesis of deoxyoligonucleotides.[7] Although it has been considered that derivatives of tetrazole were scarce in nature, relatively rich natural chemistry of these heterocyclic compounds may emerge. Curiously, it has been suggested that tetrazole compounds are constituents of the tholins on Titan, the largest moon of Saturn, where they can be generated by the action of electric sparks from nitrogen and methane—the major constituents of Titan’s atmosphere.[8] The chemistry of tetrazoles as well as the methods for their synthesis are summarized in several extensive reviews.[1−3,9−11] The preferred synthetic route to tetrazoles is the reaction of nitriles with azides at high temperature. This method, a representative of a group of 1,3-polar cycloadditions, collectively termed “click chemistry” reactions (Scheme 1),[12] has been successfully carried out by heating (80−120 °C) a mixture of the neat starting compounds[13,14] or in solvents such as DMSO or DMF and even in aqueous media.[15] The reaction is catalyzed by protic acids such as ammonium salts and acetic acid or Lewis acids such as $SnCl_2$ or $ZnCl_2$.[3] The mechanism of the Zn(II)- and Al(III)-catalyzed reaction was recently studied theoretically and most likely involves coordination of the metal ion to a nitrile molecule.[16]

Scheme 1



The similar “click” reaction between azides and alkynes, catalyzed by cuprous salts, yields triazoles and

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was recently used in the synthesis of polymeric materials.[17,18]

Polymers with tetrazole pendant groups can be prepared either via the direct radical polymerization of tetrazoles containing a vinyl substituent[19,20] or by a chemical modification of polyacrylonitrile.[21,22] These polymers are polyelectrolytes with acidity similar to this of poly(carboxylic acid)s; however, in the case of poly(5-vinyltetrazole) (poly5VT), relatively stable hydrogen-bond-stabilized aggregates of adjacent monomer units are observed, which are not formed in the copolymers of 5VT with styrene (Sty).[23] This allows for the "tuning" of the polyelectrolyte behavior of polymeric tetrazoles by means of copolymerization. Tetrazole-containing polymers are thus of interest for the production of ion-exchange and chelating resins and superabsorbents. A major drawback of free radical polymerization, the classical strategy for the synthesis of polymers with pendant tetrazole groups, is that it leads to materials of poorly controlled molecular weight distribution and chain-end functionalities. More complex structures, such as block and graft copolymers, are difficult if not impossible to prepare by conventional free radical polymerization.

The introduction of the various techniques for controlled radical polymerization (CRP) opened new possibilities for the synthesis of well-defined polymeric materials with different compositions, macromolecular architecture, and end-functional groups.[24−27] Among the other CRP methods, atom transfer radical polymerization (ATRP)[28−32] has a great potential due to the easy experimental setup, its applicability to monomers possessing various functional groups and polarities, and its tolerance to many solvents, additives, and impurities often encountered in industrial systems. ATRP yields halogen-terminated polymers that can be further used as macroinitiators for the synthesis of block copolymers[33] or as precursors of other chain-end-functionalized polymeric materials.[34] The ATRP of acrylonitrile (AN)[35,36] was thoroughly studied, and in addition to the well-defined homopolymers, several random copolymers of AN with Sty (SAN copolymers)[37] and block copolymers of AN and *n*-butyl acrylate were successfully prepared.[38] The reactive cyano group can participate in a broad variety of chemical transformations, such as hydrolysis to amides or carboxylic acids, reductions to imines, primary amines, or hydrocarbons, etc. Thus, the reactions of nitrile-containing polymers, and particularly of polyAN, have attracted significant attention.[39] Herein we report on the postpolymerization modification of well-defined homo- and copolymers (both random and block) of AN leading to tetrazole-containing polymeric materials. The direct ATRP of 5VT is expected to be more challenging due to deactivation of the copper-containing ATRP catalyst via coordination of the tetrazole rings to copper and/or protonation of the N-based ligand of the ATRP catalyst by the acidic 5VT or poly5VT. The preliminary results of the postpolymerization modification of nitrile-containing well-defined polymers leading to polymeric tetrazoles were recently reported.[40]

Experimental Section

Materials. The monomers, Sty and AN (99%, Aldrich), were purified by passing the neat liquids through a column filled with basic alumina to remove the polymerization inhibitor. CuBr and CuCl (Acros) were purified using a slightly modified literature procedure,[41] namely washing with glacial acetic acid followed by 2-propanol and drying under vacuum. The polystyrene and silica particles functionalized with initiating groups were purchased from Aldrich and Silicycle, respectively. All other reagents and solvents (purity above 98%) were used as received without further purification.

ATRP of AN. 10 mL (0.151 mol) of AN and 10 mL of ethylene carbonate were mixed in a Schlenk flask, and the mixture was degassed by three freeze−pump−thaw cycles. The flask was then filled with nitrogen while the mixture was kept frozen, and 0.1029 g (0.716 mmol) of CuBr, 0.0084 g (0.038 mmol; 5% of the total Cu) of $CuBr_2$, and 0.2354 g (1.508 mmol) of 2,2′-bipyridine were quickly added. The flask was then evacuated and back-filled with nitrogen several times, and the mixture was left to thaw. The obtained homogeneous brown reaction mixture was heated to 55 °C, and 65 μL (0.754 mmol) of deoxygenated by purging with nitrogen 2-bromopropionitrile was injected. After 1.5 h the conversion reached 68% and the reaction was stopped. The polymer was dissolved in DMF, precipitated in methanol, and dried. M_n(SEC) = 39 540 g/mol; $M_w/M_n = 1.08$. PolyAN of different molecular weights could be prepared in the same manner but using different polymerization times and/or changing the ratio of monomer to initiator.

ATRP of Sty and AN. 8.9 mL (0.135 mol) of AN, 26.4 mL (0.230 mol) of Sty (63 mol % of Sty, i.e., azeotropic monomer feed composition), and 2 mL of diphenyl ether were mixed in a Schlenk flask. The mixture was degassed by three freeze−pump−thaw cycles, and the flask was filled with nitrogen while the mixture was kept frozen. 0.1432 g (1 mmol) of CuBr and 0.312 g (2 mmol) of 2,2′-bipyridine were then added. The flask was evacuated and back-filled with nitrogen several times, and the mixture was left to thaw. The obtained brown solution was heated to 80 °C, and 136 μL (1 mmol) of deoxygenated by purging with nitrogen 1-phenylethyl bromide was injected. After 20 h the conversion reached 40%, and the reaction was stopped. The mixture was diluted with THF, and the obtained solution was passed through a column filled with neutral alumina in order to remove the copper catalyst. The polymer was precipitated in methanol and dried. M_n(SEC) = 8460 g/mol; $M_w/M_n = 1.08$.

Grafting of Sty−AN Copolymer from Particles with Attached Initiating Groups. Azeotropic monomer feed composition was again polymerized, and 4-toluenesulfonyl chloride was added as a sacrificial initiator. The ATRP catalyst contained 5% of $CuCl_2$, and the ratio of the reagents was $[Sty]:[AN]:[CuCl]:[CuCl_2]:[bpy]:[Si\text{-}SO_2Cl]:[4\text{-}MeC_6H_4SO_2Cl] = 630:370:6:0.3:12.6:1:1$. Anisole (8 vol %) was added to the reaction mixture as an internal standard for determination of conversion. The reaction was carried out for 73 h at 80 °C. The conversion reached 10.5%, and the free polymer derived from the sacrificial initiator was analyzed by SEC: $M_n = 3600$ g/mol; PDI = 1.35. In the grafting of SAN copolymer from particles modified with 2-bromoisobutyrate groups, CuBr/bpy was utilized as the catalyst and no $CuBr_2$ was added; ethyl 2-bromoisobutyrate (EBiB) was employed as the sacrificial initiator. In this case reactions were faster, but overall control over polymerization was better. The other reaction conditions were similar to those described for the sulfonyl chloride-modified particles.

Chain Extension of PolyAN Macroinitiators with Sty. In a 25 mL Schlenk flask, 1 g of polyAN−Br macroinitiator of DP = 39 (0.25 mmol Br) was dissolved in 18 mL of deoxygenated DMF under a nitrogen atmosphere. 11.2 mL (10 mmol) of deoxygenated Sty, 100 μL (0.5 mmol) of *N,N,N′,N″,N″*-pentamethyldiethylenetriamine, and 0.8 mL of anisole were then added, and the mixture was degassed by three freeze−pump−thaw cycles. 0.0496 g (0.5 mmol) of CuCl was then added under nitrogen flow. The reaction was carried out at 90 °C for 12 h. Conversion was 24%. The polymer was precipitated in 200 mL of a methanol/water mixture, washed three times with 100 mL of the same solvent mixture, filtered, and dried. M_w/M_n of the product was 1.10 determined by SEC, and composition was $(AN)_{39}(Sty)_{90}$, determined by elemental analysis (calcd/found % C: 87.85/87.88; % H: 7.37/7.56; % N: 4.77/4.67).

Table 1. Grafting of SAN Copolymers from Initiating-Group-Modified Particles[a]

particles (size)	loading (mmol of X/g)	reaction time (h)	conversion	M_n (SEC) (g/mol)	PDI
PSty−SO_2Cl (149−74 μm)	1.8	101.5	0.12	6300	1.16
SiO_2−SO_2Cl (40−63 μm)	0.93	73	0.11	3600	1.35
SiO_2−BiB (irregular)	0.14	4.5	0.17	7400	1.17

[a] Conditions: sulfonyl chloride-initiated systems: 80 °C; [Sty]:[AN]:[CuCl]:[$CuCl_2$]:[bpy]:[particle-SO_2Cl]:[4-$MeC_6H_4SO_2Cl$] = 630:370:6:0.3:12.6:1:1. 2-Bromoisobutyrate-initiated polymerization: 80 °C; [Sty]:[AN]:[CuBr]:[bpy]:[particle-BiB]:[EBiB] = 630:370:6:12:1:1.

Preparation of Tetrazole-Containing Polymers from PolyAN-Based Precursors. The homo- or copolymer (either random or block) of AN was dissolved in DMF (1−3 g in 20 mL of solvent). NaN_3 and anhydrous $ZnCl_2$ (4 equiv vs the nitrile groups) were added, and the reaction mixture was stirred at 120 °C for 48−50 h. After cooling to 60 °C, 15 mL of diluted HCl (1:10 by volume in water) was added, and the reaction mixture was kept at this temperature for 3−5 h. The (co)polymer of 5VT thus obtained was then precipitated in excess of the same aqueous HCl solution, filtered, washed on the filter with the HCl solution and water, and dried.

Analyses. Conversions were determined on a Shimadzu GC-14A gas chromatograph using a capillary column (CEC-Wax, 30 m × 0.53 mm × 1.0 μm, Chrom Expert Co.) or (in the case or grafting from particles) by NMR (with $CDCl_3$ as the solvent). The reaction solvent or specially added to the reaction mixture compound (diphenyl ether or anisole) was used as a standard for the calculations of conversion by both techniques. The samples were then filtered through a short column filled with alumina followed by a 0.2 μm PTFE filter, and the solutions were used for determination of molecular weights. Size exclusion chromatography (SEC) measurements were conducted using DMF as the eluent (flow rate 1 mL/min, 50 °C) with a series of three Styrogel columns (10^5, 10^3, 100 Å; Polymer Standard Services) and a Waters 2410 differential refractometer. Diphenyl ether was used as the internal standard. Polystyrene standards were employed for the SEC calibration. IR spectra of the polymers (KBr pellets or films cast from acetone or DMF on KBr or NaCl plates) were recorded on ATI Mattson Infinity series FTIR spectrometer. NMR spectra of the polymer solutions in acetone-d_6 or DMF-d_7 were collected (ca. 15 000 scans) on a Bruker Avance 300 MHz spectrometer. Thermogravimetric analysis (TGA) experiments were performed with samples weighing about 5 mg placed in aluminum pans, using Polymer Laboratories TG1000 instrument operating in the 20−800 °C temperature range, under nitrogen, at heating rate of 10 °C/min. The polymers were washed repeatedly with methanol or ether and then dried under vacuum at 60−80 °C for several hours prior to the TGA measurements. All TGA measurements were repeated at least twice to check for reproducibility.

Results and Discussion

The 1,3-dipolar cycloaddition of azide to organic nitriles in the presence of a protic or Lewis acid leading to 5-substituted tetrazoles, as shown in Scheme 1, is an example of a "click chemistry" reaction.[12] The tetrazole synthesis is usually carried out at high temperatures (above 100 °C) in polar solvents such as DMF, DMSO, butanol or in aqueous media. Hydrazoic acid can be directly used to form the azole ring, but since it is a highly toxic and explosive substance, other acids are preferably employed, in conjunction with a source of azide. Examples of acidic compounds include trifluoroacetic acid, aluminum or tin compounds, and ammonium salts.[2,3,11] Zinc halides are also quite efficient, and the chloride was used in the present work.[16]

The well-defined starting polymeric materials, namely, a homopolymer of AN, a random Sty−AN (SAN) copolymer, and a block copolymer of AN and Sty, as well as silica or polySty particles grafted with polySAN, were prepared by ATRP. In the case of the block copolymer, the polyAN−Br macroinitiator was synthesized first, and then it was chain-extended with the second monomer, Sty. This order is important to ensure fast initiation from the macroinitiator—a prerequisite for the efficient synthesis of a copolymer with a narrow molecular weight distribution. The copolymerization of Sty and AN using soluble initiators is described in detail elsewhere.[37] When grafting of the SAN copolymer from particles was carried out, high monomer-to-initiator ratios were used, and the reactions were stopped at relatively low conversion (<20%),[42,43] although, unlike the case of systems using nanometer-sized initiating particles, the coupling between the large particles used in this study is not very likely to occur. The addition of free soluble (sacrificial) initiator was important not only to provide sufficient amount of soluble polymer for further analysis but also to generate deactivator in the solution through the persistent radical effect and thus improve the overall control over polymerization.[44−47]

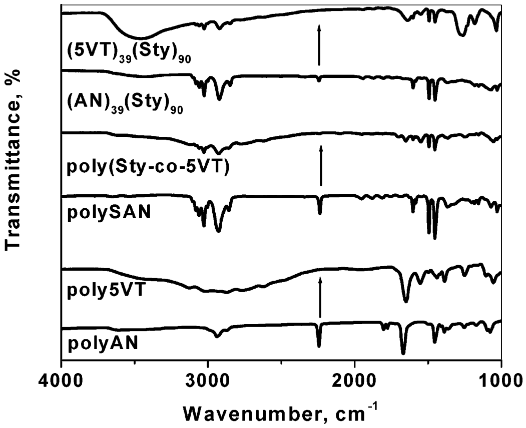

Figure 1. IR spectra of the starting polyAN (co)polymers (spectra 1, 3, and 5 from bottom to top) and of the poly5VT-unit-containing products of their modification using a "click chemistry" approach (spectra 2, 4, and 6).

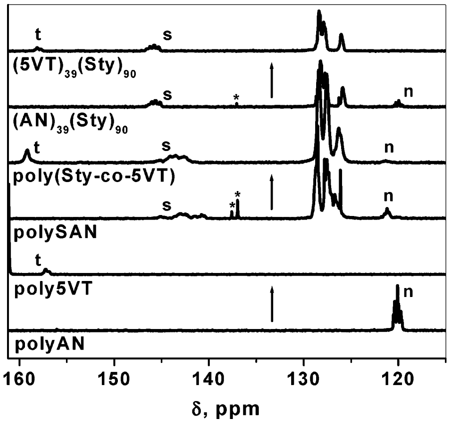

Figure 2. ^{13}C NMR spectra of the starting polyAN (co)polymers (spectra 1, 3, and 5 from bottom to top) and of the polymeric tetrazoles prepared from them (spectra 2, 4, and 6). The signals of the quaternary carbon atoms from the tetrazole and Sty rings are designated with "t" and "s", respectively, and from the nitrile group with "n". Impurity signals are marked with an asterisk.

Table 2. TGA of AN-Containing Precursors and the Polymeric Tetrazoles Derived Therefrom

entry	polymer	$T_{\mathrm{d,onset}}$, °C	$T_{\mathrm{d,10\%}}$, °C^a	$T_{\mathrm{d,max1}}$, °C^b	$T_{\mathrm{d,max2}}$, °C^b	weight loss, %^{c}
1	polyAN	255	277	272		53
2	poly5VT	120^d	276	237		87^d
3	poly(AN-*b*-Sty)	296	372	319	424	93
4	poly(5VT-*b*-Sty)	181	270	233	414	94
5	polySAN	303	354	396		96
6	poly(Sty-*co*-5VT)	196	239	230	382	95
7	PSty-SO_2−polySAN	260	348	397		97
8	PSty-SO_2−poly(Sty-*co*-5VT)	184	244	229	392	92
9	SiO_2-iB−polySAN	236	351	363		32
10	SiO_2-iB−poly(Sty-*co*-5VT)	188	342	225	368	33

[a] Temperature at which 10% of the sample weight has been lost. [b] Temperature of highest decomposition rate as determined from the maximum in the first derivative of the TGA curve. In the cases when two peaks were observed, they are indexed with the subscripts 1 and 2. [c] For the temperature range 25−800 °C. [d] Because of "explosive" decomposition of the polymer, it was difficult to reproduce the results within ±15 °C. The average value from five measurements is given in the table.

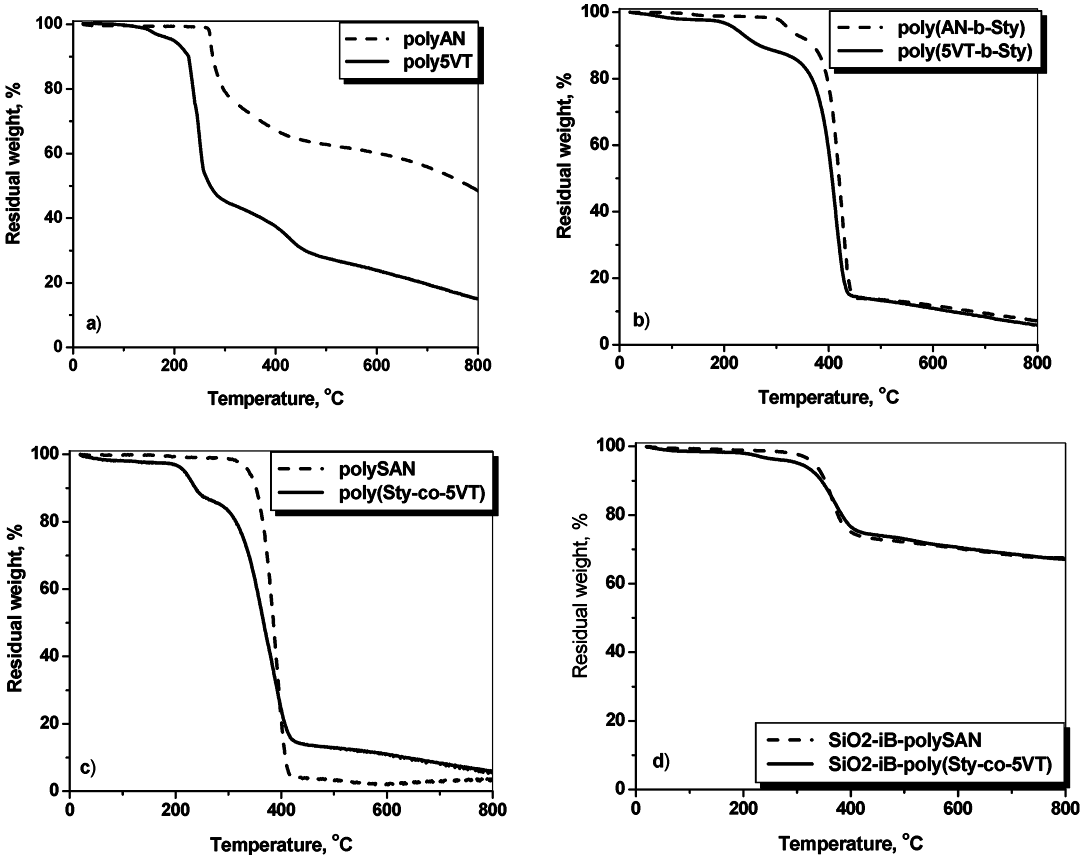

Figure 3. TGA curves of well-defined polymeric tetrazoles and the corresponding AN-based precursors: (a) homopolymers, (b) block copolymers, (c) random copolymers, and (d) supported random copolymers.

The results from the grafting from experiments are presented in Table 1. In all cases, the reactions yielded well-defined polymeric materials.

The (co)polymers used for the postpolymerization modification leading to 5VT copolymers were characterized by IR and ^{13}C NMR spectroscopy (Figures 1 and 2, respectively). The former technique was applied to the characterization of all tetrazole-containing materials (including the particles), while the latter was used only in the case of free, soluble, polymers. The nitrile group from the AN unit in the precursor (co)polymers is clearly visible by both spectral methods. This group absorbs at ca. 2240 cm^{-1} (ν_{CN}) in the IR region, and an easily distinguishable peak of the quaternary carbon atom is observed at 120 ppm in the NMR spectra.

The disappearance of the spectral signal of the nitrile group during the chemical transformation shown in Scheme 1 was used to monitor the degree of conversion and to optimize the reaction conditions. For instance, when 2 equiv of NaN_3 and $ZnCl_2$ vs nitrile from a SAN copolymer was used and the reaction time was 40 h, about 60% of the nitrile groups were converted to tetrazole. When the ratio of azide and Lewis acid to nitrile was increased to 4 and the reaction was carried out for 50 h, the modification was much more efficient. No unreacted cyano groups could be seen in the IR spectrum of the obtained product, and only insignificant signal at 120 ppm was evident in the NMR spectrum. The "click" reaction was slightly less efficient for the case of modification of SAN-coated particles. Although a significant decrease of the IR absorbance at 2240 cm^{-1} was observed in the particles treated with sodium azide and zinc chloride, in all cases unreacted nitrile groups were still present. In the other polymeric tetrazole syntheses, the same ratio of the reagents and reaction temperature were used. Figures 1 and 2 indicate the complete chemical modification of both polyAN and the block copolymer $(AN)_{39}(Sty)_{90}$. The formed tetrazole ring has a characteristic IR absorbance at 3400−3000 cm^{-1} (associated N−H), 2800−2300 cm^{-1} (N^+−H), and 1555 cm^{-1} ($\nu_{C=N}$). In the NMR spectrum, a new peak corresponding to the quaternary carbon atom of the azole ring was observed at 157 ppm.[21]

The solubility of the tetrazole-containing polyacids was distinctly different if compared to the AN-unit-containing precursor polymeric materials. Thus, polySAN is soluble in chloroform, toluene, THF and insoluble in protic solvents. The ionomer with 5VT units prepared from polySAN is soluble in methanol and swells in water. The homopolymer of 5VT (synthesized from polyAN) dissolved well in aqueous sodium hydroxide solution.

The synthesized polymers with pendant tetrazole groups were further characterized by TGA, and the results are compared to the nitrile-based precursors (Table 2 and Figure 3).

The thermal decomposition of the poly5VT derived from polyAN in nitrogen atmosphere (heating from 50 to 280 °C) was accompanied by a significant volume change due to the evolution of large amount of gases. The maximum decomposition rate was observed at 237 °C. It is reported that under air, at a heating rate of 5 °C/min, poly5VT decomposes thermally in two stages, the first being the degradation of the azole ring ($T_{d,max} = 291$ °C) and the second the thermooxidative destruction of the polymeric residue ($T_{d,max} = 342$ °C).[48] In the polymer studied by us the second peak was not observed since all TGA experiments were carried out under a nitrogen atmosphere. The first decomposition peak was observed at lower temperature compared to the literature value, which can be attributed to the higher heating rate used in our experiments. Indeed, it was shown that the gas-release curves of poly5VT decomposition are shifted toward lower temperatures as the heating rate was increased.[48] The gaseous products of the thermolysis of poly5VT under argon contain nitrogen (major component), hydrogen azide, and methane, and the exact composition as well as the mode of decomposition depends on the heating rate. When the heating rate was as high as 40 °C/min, explosive decomposition of the polymer was observed.[48] In summary, the polyAN precursor was thermally significantly more stable than the polymeric tetrazole (see entries 1 and 2 in Table 2 and Figure 3a).

A weight loss from all other synthesized polymeric tetrazoles could also be readily observed in the thermograms at 200−250 °C, which is in agreement with literature data.[21,48] In all cases, the tetrazole-containing polymers decompose at lower temperature compared to the AN-based precursors. The SAN random copolymers (both free and supported on particles) decomposed at around 360−396 °C (Table 2, entries 5, 7, and 9; Figure 3c,d), which compares well to the literature value for polySAN ($T_{d,max} = 390$ °C for copolymers of molecular weights ranging from 1×10^4 to 7.4×10^5 g/mol[49]). Since silica is stable under the heating conditions, a residual weight of about 30% was observed when heating the silica−polymer composite materials. The polystyrene particles decomposed at these conditions, as evidenced from the results in Table 2.

Conclusions

Well-defined homo- and copolymers (both random and block, including supported polymers on polystyrene or silica particles) of AN were synthesized using copper-mediated ATRP. To obtain a low-polydispersity Sty−AN block copolymer, the polyAN block was synthesized first, and the obtained polyAN−Br macroinitiator was chain-extended with Sty. All nitrile-group-containing polymeric materials were modified to the corresponding tetrazoles using the reaction with sodium azide and zinc chloride in DMF. The optimum results were achieved when the reaction was carried out at 120 °C for 50 h using a ratio of the reagents NaN_3:$ZnCl_2$:RCN equal to 4:4:1. The tetrazole-based polyacids prepared by this “click chemistry” reaction were characterized by IR and ^{13}C NMR spectroscopy. The 5VT homopolymers and random copolymers had markedly better solubilities in protic solvents than the starting materials being soluble in alkaline aqueous solutions. The polymeric tetrazoles were significantly less thermally stable than the AN-based precursors (the onset decomposition temperatures of the tetrazoles being lower by more than 100 °C).

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