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Controlled Free-Radical Copolymerization of *N*-vinyl succinimide and *n*-Butyl acrylate via a Reversible Addition–Fragmentation Chain Transfer (RAFT) Technique

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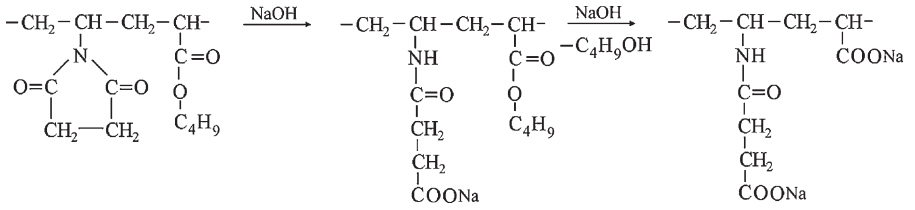
Summary: Copolymerization of N-vinyl succinimide and *n*-butyl acrylate in the presence of dibenzyl trithiocarbonate as a reversible addition-fragmentation chain transfer agent was investigated. The linear dependence of molecular mass on conversion and low values of polydispersity index confirmed pseudo-living mechanism of the process. For the first time the soluble copolymers of N-vinyl succinimide and *n*-butyl acrylate with high composition homogeneity have been synthesized by copolymerization in bulk. The copolymerization kinetics was studied by NMR ^{1}H spectroscopy; the reactivity ratios were determined: $r_{VSI} = 0.11$, $r_{BA} = 2.54$. The copolymer microstructure was estimated; it was shown that in conditions of RAFT polymerization gradient copolymers enriched with BA on the tails of the macromolecule and with VSI in the middle can be obtained. The method of elimination of trithiocarbonate fragment by the reaction with an excess of AIBN was proposed leading to formation of the simplest gradient structure of N-vinyl succinimide – *n*-butyl acrylate copolymer.

Keywords: kinetics; microstructure; molecular-mass distribution; RAFT polymerization; reactivity ratios

Introduction

(Co)polymers based on N-vinylsuccinimide (VSI) cause intense interest due to possibility of application as hydrophilic non-toxic materials in medicine. Such copolymers can be easily modified by alkaline hydrolysis resulting in conversion of VSI units to the N-vinylsuccinimidic acid (VSA) units; the typical example is given below:[1]



The carboxylic groups attached to the main chain via $-NH-C(O)-CH_2-CH_2-$ spacer permit to bind low molecular compounds including medicinal products to the polymers, leading to various advantages of such polymeric drug conjugates, for instance, their prolonged action *in vivo*.

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However, a strong problem arises during production of VSI copolymers at high conversions: due to huge difference in reactivity ratios of VSI and acrylate comonomers, which are most commonly used in copolymerization, the composition heterogeneous copolymers are formed that influences noticeably on the properties of the final product. Meanwhile the copolymer microstructure and composition heterogeneity are of great importance due to its influence on the reactions of addition of low molecular compounds to carboxylic groups of modified VSI copolymers and on macromolecules behavior in solutions. To overcome these problems we for the first time have applied RAFT technique to the copolymerization of VSI and *n*-butyl acrylate (BA). Previously we have shown that BA homopolymerization can be controlled by using dibenzyl trithiocarbonate (BTC) as a RAFT agent.[2,3]

Experimental Part

VSI was synthesized according to procedure described in [4] and was recrystallized from 2-propanol. BA was purified via distillation under reduced pressure; AIBN was recrystallized from ethanol and stored in a freezer until needed. BTC was synthesized according to [5] and characterized by ^{1}H and ^{13}C NMR. Samples for copolymerization were prepared by dissolving of calculated amounts of VSI, AIBN, and BTC in BA. The synthesis was carried out in a 10-mL glass cylindrical with round bottom ampoule in an inert argon atmosphere at 80 °C. After required periods of time the samples were taken by syringe from reaction mixture; the samples were frozen and then the copolymers were extracted by precipitation in diethyl ether and multiply washing with warm water. The content of residual monomers was controlled by ^{1}H NMR. The spectra were recorded using Bruker DRX operating at 500 MHz in DMSO-d_6, at 25 °C with TMS as internal standard. Molecular mass characteristics of copolymers were determined by SEC in THF at 35 °C using Waters liquid chromatograph equipped with refractometric and UV-detectors and columns packed with ultrastiragel with the pore size 10^3, 10^5 Å and linear column. Molecular masses were determined using PS-standards.

Results and Discussion

The main aim of this study was to obtain soluble poly(VSI-BA) with high composition homogeneity by polymerization in bulk. This task cannot be achieved using conventional free-radical polymerization because of (*a*) the chain transfer reaction to VSI cycle methylen protons leading to cross-linked product[1] and (*b*) a great difference of VSI and BA reactivity ratios.

In our earlier publications we reported about copolymerization of VSI with BA proceeding in conditions of conventional free-radical copolymerization in various solvents: DMSO, acetic ahhydride,[6,7] dichloroethane, pyridine,[8] triethyl- and tributyl amines,[9] benzyl alcohol,[10] and in the conditions of complex-radical polymerization[10]. The values of reactivity ratios calculated using the Yezrielev-Brokhina-Roskin (YBR) [11] and Kelen–Tüdõs (KT) [12] methods are given in Table 1. Independently from copolymerization conditions BA is a more reactive monomer in copolymerization comparing to VSI, as a result at low conversions the copolymer is

Table 1.
Reactivity ratios of VSI (M_1) with *n*-butyl acrylate (M_2).

Solvent	YBR		KT	
	r_1	r_2	r_1	r_2
DMSO	0.07	2.76	0.07	2.78
DMSO + $ZnCl_2$	0.006	3.47	0.004	3.47
Dichloroethan[a]	0.15	1.55		
Pyridine	0.26	1.86	0.29	1.86
Triethylamine	0.07	2.67	0.07	2.67
Tributylamine	0.02	1.61	0.05	1.61
Acetic anhydrid	0.05	0.94	0.05	1.01
Benzyl alcohol	0.02	1.93	0.004	2.06
Benzyl alcohol + $AlCl_3$	0.01	1.48	0.001	1.56
In bulk (RAFT)	0.11	2.54	0.10	2.53

[a]– calculated using the universal method [13]

enriched with BA. With increase of total monomer conversion the monomer feed ratio changes strongly and at about 70% of total monomer conversion all BA is consumed, afterwards the homopolymerization of VSI takes place, resulting in formation of strongly composition heterogeneous product.

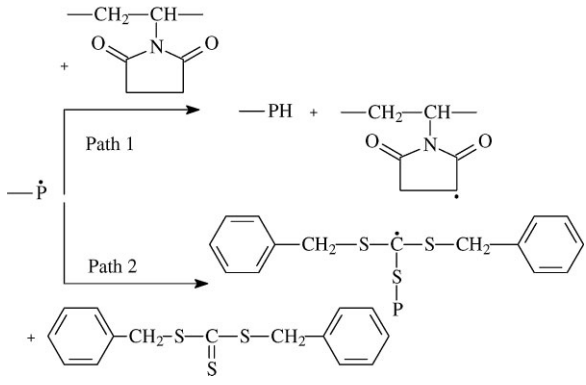
RAFT technique seems to be the most efficient way to solve both of the problems of VSI (co)polymerization denoted above. In particular, the addition of BTC as a RAFT agent to the reaction mixture turns the polymerization to path 2 as shown on the following Scheme 1:

Technically there is no any difference between realization of conventional and RAFT polymerization, but the mechanism of the process differs dramatically and can be described in the following way (Scheme 2):

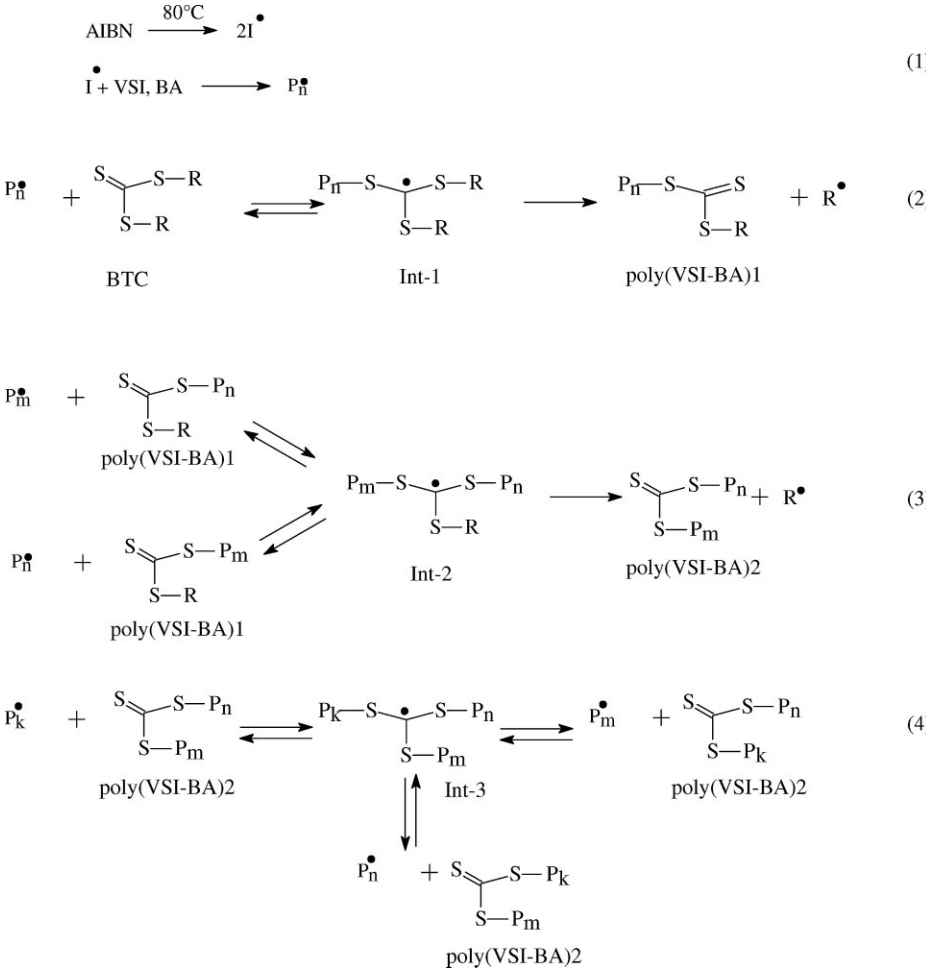
The initiation and propagation steps (1) are identical to the classic process. At the second step (2) the propagating radical adds to C=S bond of BTC to produce an intermediate carbon-centered radical Int-1, which can either regenerate the initial propagating radical or release the leaving group, in this case, benzyl-radical. Benzyl-radical is more stable than the propagating one but it is capable of polymerization reinitiating. As a result the new poly-RAFT agent poly(VSI-BA)1 is formed, which reacts with new propagating radical forming another poly-RAFT agent poly(VSBA)2 containing both polymer radicals P_n and P_m (step (3)). As it was shown by the numerous examples the reactivity of poly-RAFT agents in transfer reaction is much higher than that of the initial RAFT agent.[14] On the next stage (4) poly-RAFT agent participates in analogous repeating addition-fragmentation reactions, which release the propagating radicals capable to grow. The chain termination in RAFT process occurs like in the conventional polymerization, but plays no essential role in formation of the polymeric chains.

Hence, using RAFT technique in the case of VSI (co)polymerization allows to solve a complex problem of synthesis of soluble not cross-linked polymers with high composition homogeneity and narrow molecular-mass distribution. It is important that the presence of RAFT agent does not influence on the monomer reactivity but confines the composition heterogeneity within a macromolecule.

The copolymerization of VSI with BA in the presence of BTC was carried out under the following conditions: $[BTC] = 10^{-2}$ mole/l, $[AIBN] = 10^{-3}$ mole/l, the monomer feed ratio VSI:BA changes from 25:75 to 50:50 (mol.%). For the first time we succeeded to determine the reactivity ratios for this monomer pair in bulk RAFT copolymerization; their values given in Table 1 were calculated on the base of the conversion dependence of copolymer composition obtained at different comonomer feed



Scheme 1.
The paths of propagating radical transformations.



Scheme 2.
Mechanism of RAFT polymerization in the presence of trithiocarbonates.

ratios (Figure 1) according YBR and KT algorithms.

Monitoring of monomer concentrations, copolymer composition and conversion was carried out by NMR ^{1}H spectroscopy; the typical NMR ^{1}H spectrum of reaction mixture, the signals assignment and the integrated intensities are given on Figure 2 and Table 2.

The values of reactivity ratios calculated for bulk RAFT copolymerization of VSI and BA are close to the values determined earlier in solution copolymerization in DMSO and triethylamine (Table 1); it is not surprising due to electron-donor nature of the monomers. As is seen on Figure 1, the copolymer obtained in RAFT copolymerization at initial conversions also is strongly enriched with BA, and the content of BA units in copolymer decreases with increase of total monomer conversion. The obtained results indicate that in the wide range of feed ratios the probability of BA monomer unit locating on the end of the propagating radical is noticeably higher then VSI monomer unit. Hence we may expect a good control over molecular masses in copolymerization as we have observed before in BA homopolymerization.[2,3]

Indeed, as it is seen from Figure 3a, with increase of the polymerization time the

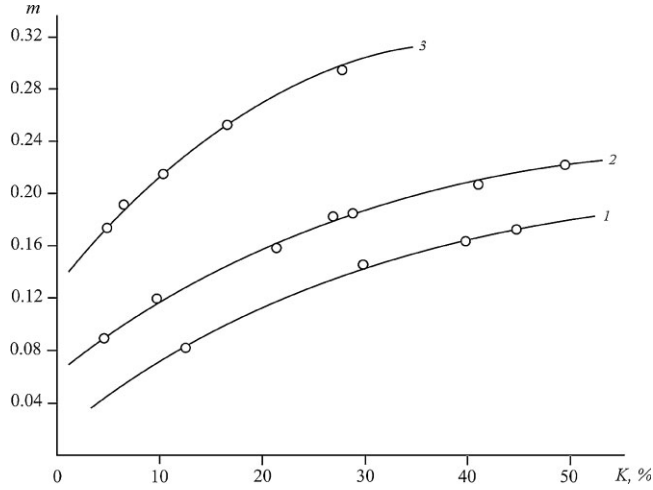


Figure 1.
The dependence of copolymer composition *m* (VSI, mole fraction) *vs* conversion *K* obtained at different comonomer feed ratios: 25 (*1*), 37 (*2*) and 50 (*3*) mol.% VSI.

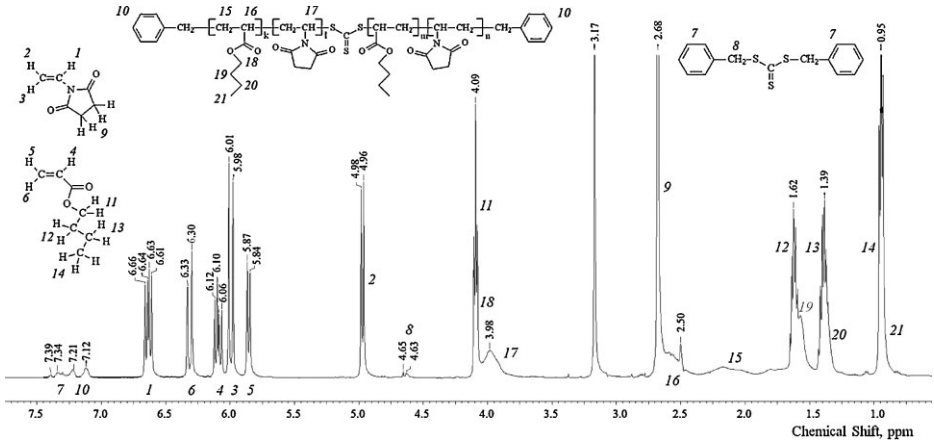


Figure 2.
The NMR ^{1}H spectrum and its signals assignment of the reaction mixture at copolymerization of VSI and BA. [VSI] =[BA] =3.64 mole/l, [BTC] = 10^{-1} mole/l, [AIBN] = 10^{-3} mole/l, conversion 28%, 80°C.

molecular masses of the copolymers formed successively grow; essentially that polydispersity index is extremely low (1.13–1.15). This result allows concluding that copolymerization proceeds in a controlled mode.

In a supplementary experiment a copolymer (1.3×10^{-4} mole/l) was heated in

Table 2.
The integrated intensities of the signals in the reaction mixture NMR spectrum.

Signal number according to Figure 2	**7 + 10**	**1**	**6**	**4**	**3**	**5**	**2**	**8**
Intensity	1.00	3.02	2.25	2.21	3.14	2.31	3.06	0.17
Signal number according to Figure 2	**11**	**17**	**9 + 16**	**15**	**12 + 19**	**13 + 20**	**14 + 21**	
Intensity	4.49	2.89	15.47	2.51	8.51	7.62	10.65	

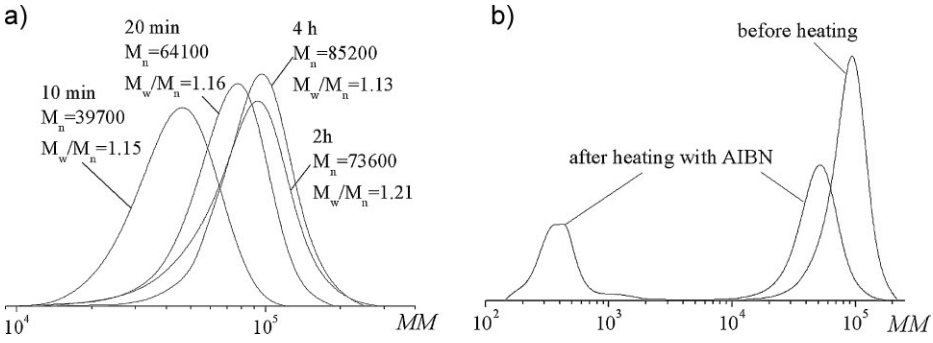
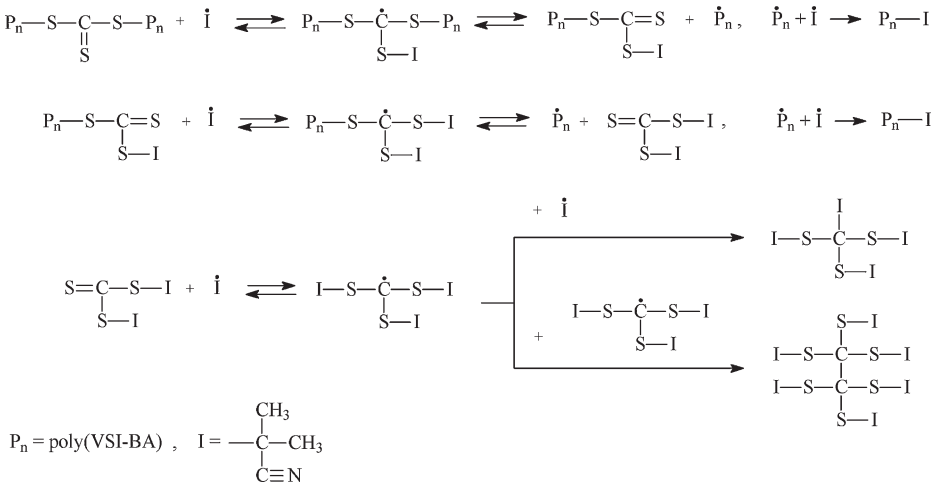


Figure 3.
SEC traces of (*a*) copolymers formed in bulk copolymerization of VSI and BA in the presence of BTC at 80 °C. [BA]/[VSI] = 75/25 mol.%, [BTC] = 10^{-2} mole/l, [AIBN] = 10^{-3} mole/l; (*b*) copolymer before and after heating with excess of AIBN.

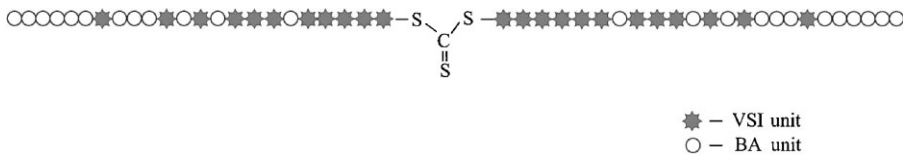
inert solvent (benzene) with excess of AIBN (3×10^{-1} mole/l) at 80°C during 24 h (Figure 3b). The Scheme 3 provides mechanism of this process. According to this scheme, if trithiocarbonate group (−S−C(=S)−S−) is located in the middle of the polymeric chain, but not on its tail, after heating with the initiator in the absence of monomer the molecular mass of the polymer should decrease in half. If it is located on the tail, molecular mass should remain practically the same. As it is seen from Figure 3b, the molecular mass of the copolymer decreases from $M_n = 75900$ to $M_n = 43400$, which confirms that trithiocarbonate group is located in the middle of the chain. Low molecular mass products are formed as a result of radicals recombination reactions and the pathway of their formation is shown at the Scheme 3. Hence according to the scheme the initial polymeric chain has a structure P_n−S−C(=S)−S−P_n.

The obtained results allow to conclude that due to (*a*) living mechanism of the process, (*b*) a great difference in monomer reactivity ratios and (*c*) location of trithiocarbonate group in the middle of the chain the composition homogeneous copolymer should form in RAFT copolymerization of



Scheme 3.
The mechanism of interaction of copolymer containing trithiocarbonate group with excess of AIBN in benzene.

VSI and BA of the gradient structure given below:



CS_3-fragment is close to the middle of macromolecule, the composition of both the polymeric substituents P_n changes from practically homo-polyVSI adjoining to the trithiocarbonate group to the copolymer enriched with BA units at the tails. After removing CS_3-fragment as it is shown above the simplest gradient structure can be obtained:

For further confirmation of the gradient structure we have calculated the probability of dyad (f_{ij}) and triad (f_{ijk}) formation as well as the average statistical length of the sequences of *n* monomer units of VSI (Z_1) and BA (Z_2); the results are summarized in Table 3 and Figure 4. As is seen with the increase of VSI content in monomer mixture the slow growth in the probability of the formation of dyads of M_1–M_1 and M_1–M_2 is observed, and the calculations predict that the long sequences $(BA)_n$ are alternated with single VSI units (Table 3). Similarly with increasing of VSI containing in the monomer mixture the fraction of triad f_{222} remains high up to about 50 mol.% of VSI, while the fraction of triad f_{111} remains close to zero (Figure 4a).

More obviously the tendency to units alternating in the copolymer chain can be seen from the dependence of the summary probability of formation of a monomer unit between the units of the other monomer (R_{11} and R_{21}) *vs* the monomer mixture composition (Figure 4b). The highest probability of units alternation is observed at VSI containing of about 80 mol.%. It agrees with the maximum of the probability of formation of isolated units (R_{11} and R_{21}) and the minimum of the summary probability of formation of *n* units sequences ($R_{1n} + R_{2n}$): $(R_{1n} + R_{2n}) = (1 - R_{11} - R_{21})$, $n \geq 2$.

Basing on the results of calculations and the experimental data on the monomers concentration changing during the copolymerization, it is possible to predict the change of the structure of the polymeric chains in the course of the process (Table 4). As it is seen in copolymerization of equimolar monomer mixture at the beginning of the process

Table 3.
The formation probability of dyad f_{ij} and the average statistical length of the blocks of repeated units of VSI (Z_1) and BA (Z_2) obtained in RAFT copolymerization at different monomer feed ratios.

VSI, mol.%	f_{11}	f_{22}	$f_{12} = f_{21}$	Z_1	Z_2
10	0	0.923	0.038	1.0	23.9
20	0.001	0.841	0.079	1.0	11.2
30	0.004	0.754	0.121	1.0	6.9
40	0.008	0.662	0.165	1.1	4.8
50	0.015	0.563	0.211	1.1	3.5
60	0.027	0.458	0.257	1.2	2.7
70	0.049	0.346	0.302	1.3	2.1
80	0.095	0.226	0.339	1.4	1.6
90	0.215	0.101	0.342	2.0	1.3

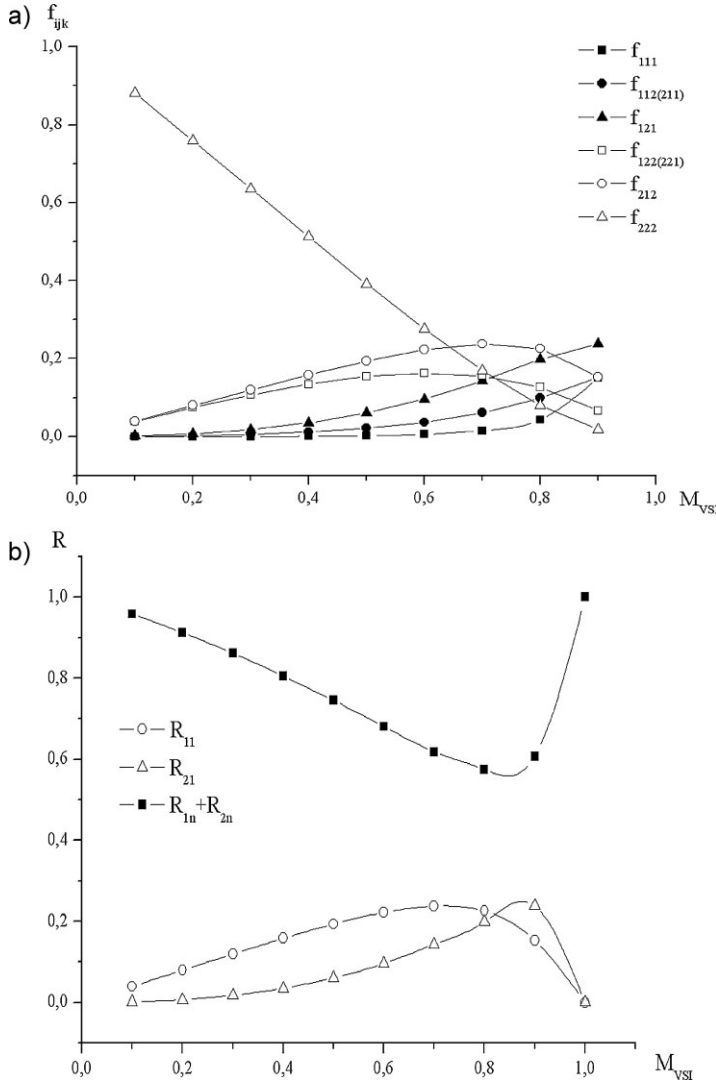


Figure 4.
The probability of triad formation f_{ijk} (*a*), and the probability of formation of isolated units R_{i1} and the summary probability of formation of *n* units successions ($R_{1n} + R_{2n}$) (*b*) in VSI (1) and BA (2) copolymers obtained at the monomer mixture composition M_{vsi} (VSI mole fraction) under the conditions of RAFT copolymerization.

Table 4.
The probability of the average statistical length of the blocks of repeated units of VSI (Z_1) and BA (Z_2) obtained at different conversions in RAFT copolymerization of equimolar monomer mixture.

Conversion,%	M_{VSI}	M_{BA}	Z_1	Z_2
0	0.5	0.5	1.1	3.5
25	0.57	0.43	1.1	2.9
50	0.65	0.35	1.2	2.4
60	0.73	0.27	1.3	1.9
75	1	0		0

the isolated units of VSI are alternated with blocks consisting of 3–4 units of BA, then the sequence of BA units decreases, and after 75% total conversion BA is consumed, and VSI units are added to the polymeric chain.

Hence, we may estimate the change of macromolecular chain microstructure with progress in monomer conversion; results are given on Figure 5.

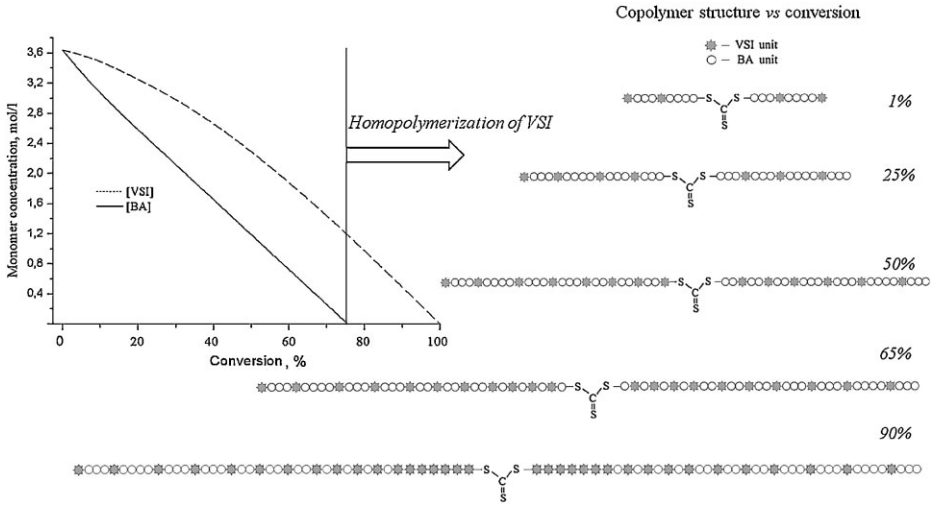


Figure 5.
The dependence of the monomers concentrations and the copolymer structure vs conversion in RAFT copolymerization of VSI and BA.

Conclusion

In the present study we suggest the procedure of the synthesis of gradient copolymers of VSI and BA in bulk RAFT copolymerization. The copolymer remains soluble, not cross-linked, with high composition homogeneity up to the limited monomer conversions. Basing on the structure of RAFT agent and the monomer reactivity ratios it may be concluded that copolymer formed at limited conversions is enriched with BA on the tails of the macromolecule, while moving to the middle of the chain the composition changes and in the centre of the chain blocks of pure VSI are located.

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