Rapid Communication

Significant Effect of Hydrogen-Bonding Interaction on Syndiotactic-Specificity in Radical Polymerization of *N*-Isopropylacrylamide

TOMOHIRO HIRANO, HITOMI MIKI, MAKIKO SENO, TSUNEYUKI SATO

Department of Chemical Science and Technology, Faculty of Engineering, Tokushima University, Minamijosanjima 2-1, Tokushima 770-8506, Japan

Correspondence to: T. Hirano (E-mail: hirano@chem.tokushima-u.ac.jp)

Keywords: *N*-isopropylacrylamide; radical polymerization; hydrogen bond; syndiotactic; stereoregular polymer; NMR

In general, methacrylic acid derivatives such as methacrylates and methacrylamides give syndiotactic-rich polymers by a radical polymerization. Furthermore, methacrylates is one of the most intensively investigated monomers in regard of stereospecificity of polymerization and there are a lot of reports on synthesis of a wide range of stereoregular polymers not only by an anionic polymerization but by a radical polymerization. However, acrylic acid derivatives such as acrylates and acrylamides give atactic polymers regardless of polymerization conditions and there are limited reports on stereospecificity of polymerization. Therefore, it is accepted that steric interaction by □-methyl group is one of the important factors to control stereostructure of vinyl polymers.

Poly(*N*-isopropylacrylamide) [poly(NIPAAm)] has been widely investigated as

a switching device, since poly(NIPAAm) shows a lower critical solution temperature (LCST) which lies between ca. 30 and 35°C.[1-4] To control the LCST, many researchers investigated radical copolymerization of NIPAAm, because the LCST depends on the microstructure including a copolymer composition. However, although polymer properties are often significantly influenced by the stereostructure of macromolecules, there are few reports on a stereoregularity of poly(NIPAAm) since NIPAAm is also one of acrylic acid derivatives.

Recently, it was reported that stereoregular poly(NIPAAm) could be prepared by an anionic polymerization of NIPAAm, of which the acidic proton was protected. For instance, an anionic polymerization of a trimethylsilyl-protected NIPAAm derivative with *t*-C_4H_9Li/*n*-$(C_4H_9)_3Al$ in toluene at –40°C gave a highly isotactic poly(NIPAAm) with meso (*m*) diad content of 97%.[5] A syndiotactic poly(NIPAAm) with racemo (*r*) diad content of 77% was also obtained by an anionic polymerization of a methoxymethyl-protected NIPAAm derivative with 1,1-diphenyl-3-methylpentyllithium / diethylzinc in tetrahydrofuran (THF) at –78°C.[6] However, an industrial application of these methods would be difficult, since these polymerizations require extra operations such as protection of monomers and deprotection of polymers in addition to the polymerization reaction.

On the other hand, Okamoto *et al*. reported that a radical polymerization of NIPAAm in methanol at –20°C in the presence of rare-earth metal trifluoromethanesulfonates (triflates) such as yttrium triflate gave directly a highly isotactic poly(NIPAAm) with *m* diad of 92%.[7] This result indicates that it is possible to control stereospecificity of radical polymerization of acrylic acid derivatives. However, a facile synthesis of syndiotactic poly(NIPAAm) has not been achieved, and thus the direct synthesis of a syndiotactic poly(NIPAAm) *via* a radical polymerization has been desired.

We have reported that the use of amide compounds as a solvent suppresses the

intramolecular chain-transfer reaction which takes place in radical polymerizations of itaconates as a side reaction.[8] The NMR analysis demonstrated that the complex formation between an itaconate monomer and amide compounds through a hydrogen-bonding interaction is the key of the suppression of the intramolecular chain-transfer reaction. This result indicates that even a weak hydrogen-bonding interaction has a potential to control a radical polymerization reaction. Furthermore, in the last decade, some stereocontrol methods in radical polymerization with hydrogen-bonding interaction have been reported.[9-11] Therefore, we started investigating the effect of a hydrogen-bonding interaction on a stereocontrol in a radical polymerization of NIPAAm that has an amide group. Recently, we found that a syndiotactic-rich poly(NIPAAm) could be directly prepared even by a radical mechanism at low temperatures in the presence of Lewis base. Here, we report the preliminary results of the syndiotactic-specific polymerization of NIPAAm in the presence of Lewis base, although the regularity is not as high as that of an anionically prepared poly(NIPAAm).[6]

Experimental Section

N-Isopropylacrylamide (NIPAAm) was recrystallized from hexane-benzene mixture. Toluene was purified through washing with sulfuric acid, water, and 5% aqueous NaOH; this was followed by fractional distillation. Tri-*n*-butylborane (*n*-Bu_3B) as a THF solution (1.0M) and Lewis bases such as hexamethylphosphoramide (HMPA) were commercially obtained and used without further purification for polymerization reaction.

Typical polymerization procedure is as follows; NIPAAm (0.628 g, 5.5 mmol) was dissolved in toluene to prepare the 5 mL solution of 1.0 x 10^{-1} mol/L. Four milliliter of the solution was transferred to the glass ampoule and cooled at 0°C. The polymerization was initiated by adding *n*-Bu_3B solution (0.44 ml) into the monomer

solution. After 24h, the reaction was terminated with a small amount of THF solution of 2,6-di-*t*-butyl-4-methylphenol at polymerization temperature. The polymerization mixture was poured into a large amount of hexane, and the precipitated polymer was collected by filtration, and dried *in vacuo*. The polymer yield was determined from the weight ratio of the obtained polymer and the feed monomer.

The ^{1}H and ^{13}C NMR spectra of NIPAAm monomer and/or HMPA were measured in toluene-d_8 at 0°C on a JEOL EX-400 spectrometer operated at 400MHz for ^{1}H and at 100MHz for ^{13}C. The tacticities of the poly(NIPAAm)s were determined from ^{1}H NMR signals due to methylene group in chain measured in deuterated dimethyl sulfoxide (DMSO-d_6) at 150°C.

Results and Discussion

Radical Polymerization in the Presence of Lewis Bases.

Table 1 summarizes the polymerization results of NIPAAm with *n*-Bu_3B in toluene at 0°C in the absence or presence of equimolar amounts of Lewis bases. Aniline derivatives hardly affected the stereoregularity of the obtained poly(NIPAAm)s regardless of both the kind and the number of the substituents at *ortho*-position (Table1, runs 2-4). It is suggested that the aniline derivatives have no basicities enough to affect the stereocontrol in NIPAAm polymerizations.

Thus, radical polymerizations were conducted in the presence of alkylamines which exhibit more basicities than aniline derivatives. Alkylamines decreased the polymer yield and, in particular, *n*-hexylamine gave no polymer (Table 1, run 5). It is suggested that the complex formation between Lewis acid (*n*-Bu_3B) and Lewis base (alkylamine) prevent *n*-Bu_3B from initiating a polymerization reaction. However, no significant influences were observed in the stereoregularities of the obtained poly(NIPAAm)s (Table 1, runs 6 and 7). It is considered that *N*-coordinating Lewis bases have no potential to affect the stereocontrol of NIPPAm polymerizations under at

least the given conditions. Therefore, we carried out NIPAAm polymerizations in the presence of *O*-coordinating Lewis bases as harder bases, instead of *N*-coordinating Lewis bases.

The addition of *O*-coordinating Lewis bases showed the tendency of the slight increase in syndiotactic diad (Table 1, runs 8-13). This result suggests that the coordination of amide proton (hard acid) with oxygen atom harder than nitrogen atom is more effective in affecting the stereocontrol of NIPAAm polymerization. In particular, hexamethylphosphoramide (HMPA) exhibited the most significant effect among the used Lewis bases (Table 1, run 12). Furthermore, a 2-fold amount of HMPA slightly enhanced the syndiotactic-specificity and syndiotactic-rich poly(NIPAAm) with *r* diad = 63% was obtained (Table 1, run 13). Figure 1 displays ^{1}H NMR spectra of methine and methylene groups in chain of the obtained poly(NIPAAm)s (Table 1, runs 1 and 13). The syndiotacticity of 63% is the highest among those of radically-prepared poly(NIPAAm)s so far reported.

Table 1. Radical polymerization of NIPAAm with *n*-Bu_3B in toluene at 0°C for 24h in the absence or presence of Lewis bases[a]

Run	Added Lewis base	Yield	Diad tacticity / %[b]		
		%	*m*	:	*r*
1	None	>99	45	:	55
2	2-ethylaniline	>99	44	:	56
3	2-*t*-butylaniline	>99	44	:	56
4	2,6-diethylaniline	>99	44	:	56
5	*n*-hexylamine	trace			
6	di-*n*-propylamine	51	45	:	55
7	triethylamine	31	46	:	54
8	dimethyl carbonate	>99	43	:	57

9	3-methyl-2-oxazolidinone	>99	43	:	57
10	1,1,3,3-tetramethylurea	>99	42	:	58
11	trimethyl phosphate	>99	41	:	59
12	hexamethylphosphoramide	>99	38	:	62
13	hexamethylphosphoramide[c]	98	37	:	63

a.$[NIPAAm]_0 = [Lewis\ base]_0 = 1.0$ mol/L, $[n\text{-}Bu_3B]_0 = 0.1$ mol/L.

b. Determined by ^{1}H NMR signals due to main-chain methylene group.

c. $[HMPA]_0 = 2.0$ mol/L.

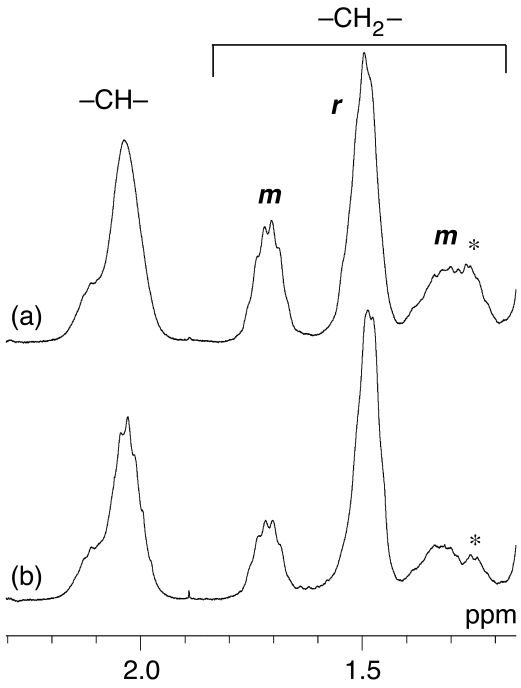


Figure 1. 400MHz ^{1}H NMR spectra of methine and methylene groups in chain of poly(NIPAAm)s prepared in toluene at 0°C in the absence (a) or presence of a 2-fold amount of HMPA (b). *: hexane.

Hydrogen-Bonding Interaction between NIPAAm and HMPA.

To examine the concernment of a hydrogen-bonding interaction to the stereocontrol in NIPAAm polymerizations, we conducted ^{1}H NMR analysis. Figure 2 shows the

expanded spectra of amide proton (N-H) of NIPAAm alone ($[NIPAAm]_0$ = 0.25 mol/L) and NIPAAm mixed with an equimolar amount of HMPA ($[NIPAAm]_0$ = $[HMPA]_0$ = 0.25 mol/L) in toluene-d_8 at 0°C. The signal due to the amide proton showed a down-field shift in the presence of HMPA as compared with that in the spectrum of NIPAAm alone (7.34 ppm –> 8.70 ppm). This result indicates that NIPAAm monomer forms a complex with HMPA through a hydrogen-bonding interaction as expected.

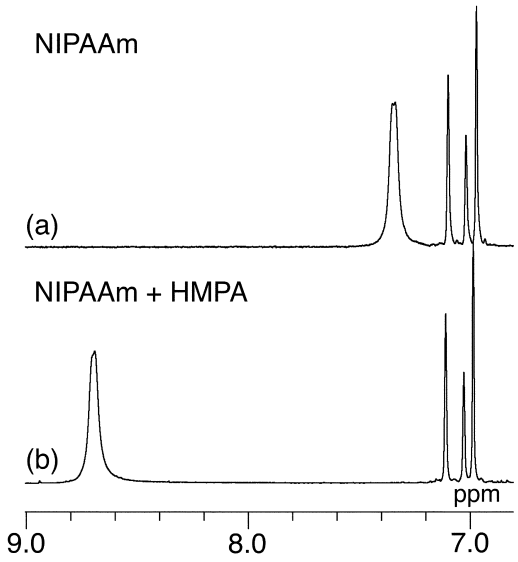


Figure 2. ^{1}H NMR spectra of amide proton of (a) NIPAAm and (b) an equimolar mixture of NIPAAm and HMPA. Measured in toluene-d_8 at 0°C.

To investigate the stoichiometry of the NIPAAm-HMPA complex, we conducted ^{13}C NMR analysis under the conditions as follows; $[NIPAAm]_0$ + $[HMPA]_0$ = 0.5 mol/L, in toluene-d_8 at 0°C. However, the chemical shift of NIPAAm alone also varied with the concentration because NIPAAm associates with each other through a hydrogen-bonding interaction. The chemical shift of carbonyl carbon showed up-field shift with a decrease in $[NIPAAm]_0$ both in the absence and presence of HMPA. On

the other hand, the chemical shift of methylene carbon showed down-field shift in the presence of HMPA, whereas that showed slight up-field shift in the absence of HMPA (Figure 3). Therefore, we applied the chemical shift of methylene carbon to Job's plot (Figure 4) to evaluate the stoichiometry with the following equation (1);[12]

$$[\text{NIPAAm - HMPA}] = \frac{\delta(CH_2{=}) - \delta(CH_2{=})_f}{\delta(CH_2{=})_c - \delta(CH_2{=})_f} \times [\text{NIPAAm}]_0 \quad (1)$$

where $\delta(CH_2{=})$, $\delta(CH_2{=})_c$, and $\delta(CH_2{=})_f$ are the chemical shifts of methylene carbon of the sample mixture, the saturated mixture, and NIPAAm alone at the corresponding concentration, respectively. The chemical shift for the saturated mixture ($\delta(CH_2{=})_c$) was calculated from the intercept of an almost linear dependence in Figure 3, since the saturation should be independence of $[NIPAAm]_0$. The maximum was observed at 0.5 of the $[NIPAAm]_0$ fraction, indicating that NIPAAm and HMPA forms 1:1 complex in this polymerization system.

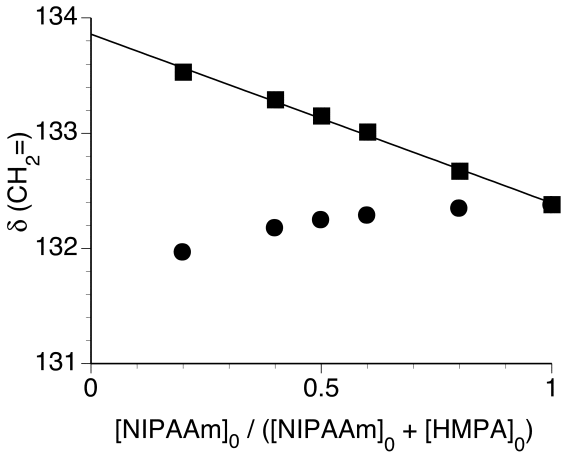


Figure 3. Changes in the methylene carbon chemical shifts of NIPAAm in the presence of HMPA (B) ($[NIPAAm]_0 + [HMPA]_0 = 0.5$ mol/L) and of NIPAAm alone at the corresponding concentration (J), measured in toluene-d_8 at 0°C.

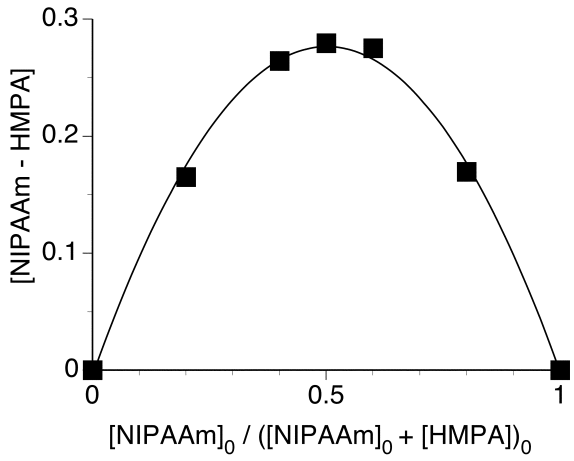


Figure 4. Job's plots for the association of HMPA with NIPAAm evaluated from the changes in the chemical shift of methylene carbon of NIPAAm.

The equilibrium constant (K) of the NIPAAm-HMPA complex was determined by changes in the ^{1}H NMR chemical shift of amide proton of NIPAAm. Figure 5 demonstrates the relationship between the change in the chemical shift and the ratio of $[HMPA]_0/[NIPAAm]_0$ with the constant concentration of $[NIPAAm]_0$ (5.0×10^{-2} mol/L) in toluene-d_8 at 0°C. The equilibrium constant (K = 44.0 L/mol) was determined by the analysis of the data in Figure 5 by a nonlinear least-squares fitting to the following equation (2):[13]

$$\Delta\delta = \frac{\Delta\delta'}{2}\left(b - \sqrt{b^2 - 4X}\right) \quad (2)$$

$$b = 1 + X + \frac{1}{(K[NIPAAm]_0)}$$

$$X = [HMPA]_0 / [NIPAAm]_0$$

where $\Delta\delta$ and $\Delta\delta$' are the changes in the chemical shift of amide proton of NIPAAm for the given solution and a saturated solution, respectively. Thus, we evaluated the degree of association (α) of NIPAAm as 0.86 (1eq.) and 0.98 (2eq.), respectively, for the actual polymerization system (cf. Table 1, runs 17 and 18).

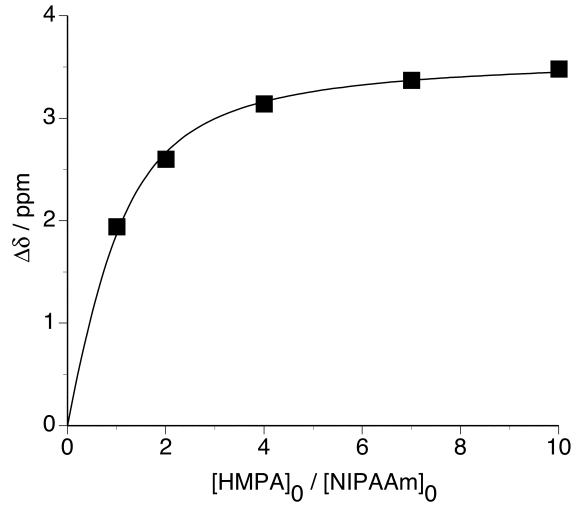
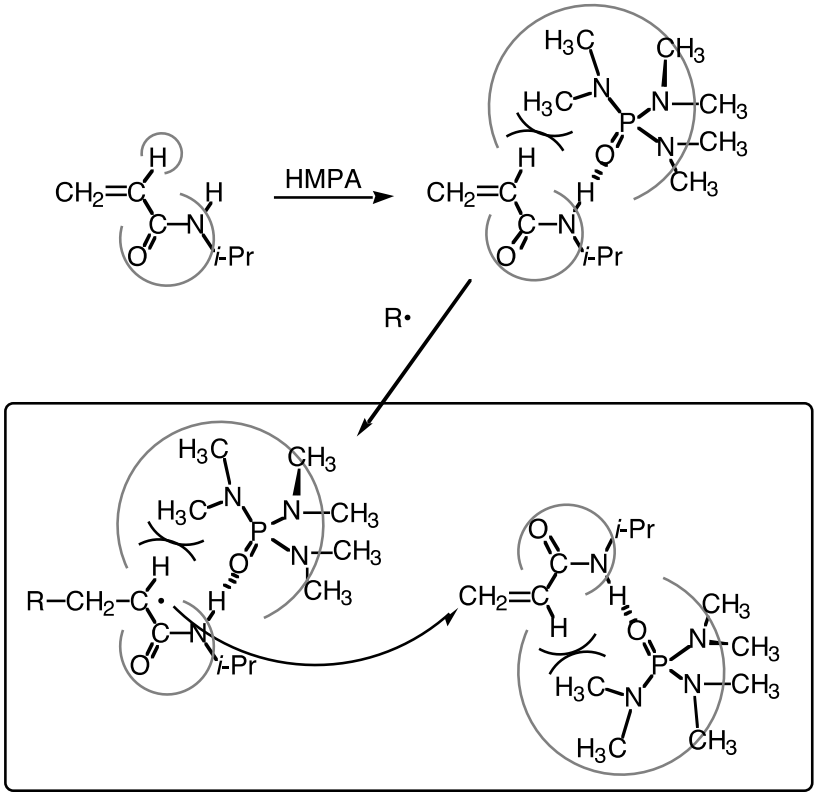


Figure 5. Changes in the chemical shift of the amide proton of NIPAAm in the presence of HMPA.

Role of HMPA in Syndiotactic-Specific Polymerization of NIPAAm.

As mentioned above, it is accepted that the steric repulsion by less bulky substituent at α-position ascribes to the difference between stereospecificities of acrylic acid derivatives (–H) and methacrylic acid derivatives (–CH_3). Thus, we propose the following mechanism for the present polymerization. First, NIPAAm forms the 1:1 complex with the added HMPA. The extended methyl groups of HMPA generate a certain steric hindrance around α-hydrogen atom, since NIPAAm favors to be *s-cis* C=C-C=O and *s-trans* O=C-N-H conformations.[14] When the complexed NIPAAm undergoes a propagating reaction, the HMPA, which coordinated to the NIPAAm monomer, would stay at the newly formed propagating chain-end. The steric hindrance generated by HMPA should be maintained even at the newly formed propagating radical (Scheme 1). As a result, the propagating reaction should proceed between the propagating radical and the monomer, both of which are coordinated by HMPA. In this case, HMPA looks to reverse the relative bulkiness between the side of α-hydrogen atom and the side of amide group in both the propagating radical and the

incoming monomer. Consequently, the amide group would play a role of less bulkier substituent instead of α-hydrogen atom and the combination of α-hydrogen atom and HMPA would behave like bulkier substituent. The amide group is bulkier than a hydrogen atom and comparable to a methyl group. Thus, it is considered that the apparent less bulky substituent, amide group, exhibited a significant steric hindrance so that syndiotactic-rich poly(NIPAAm)s were obtained even by radical polymerization of NIPAAm in the presence of HMPA.



Scheme 1. Formation of 1:1 Complex of HMPA and NIPAAm monomer and complexed propagating radical derived therefrom , and the propagating reaction between propagating radical and monomer, both of which are coordinated by HMPA.

Conclusions

We succeeded in directly preparing a syndiotactic-rich poly(NIPAAm) by a radical

polymerization utilizing a hydrogen-bonding interaction. This is the first example of a direct synthesis of a syndiotactic poly(NIPAAm), although the syndiotacticity is not as high as that of anionically prepared poly(NIPAAm). The development of stereospecific radical polymerization is expected, since the findings described in this paper indicates that even a weak hydrogen-bonding interaction is available for the stereocontrol of radical polymerizations of acrylate derivatives, having no α-methyl group which is one of the important factors to the stereocontrol in vinyl polymerizations. Therefore, further work is now under way to extend the present results to other monomers including (meth)acrylamides as well as to higher level of stereoregulation.

Acknowledgement. The authors are grateful to the Center for Cooperative Research Tokushima University for NMR measurements.

References

1. Schild, H. G. Prog. Polym. Sci. 1992, 17, 163.
2. Kikuchi, A.; Okano, T. Adv. Drug Delivery Rev. 2002, 54, 53.
3. Kawaguchi, H.; Kisara, K.; Takahashi, T.; Achiha, K.; Yasui, M.; Fujimoto, K. Macromol. Symp. 2000, 151, 591.
4. Hoffman, A. S.; Stayton, P. S.; Bulmus, V.; Chen, G.; Chen, J.; Cheung, C.; Chilkoti, A.; Ding, Z.; Dong, L.; Fong, R.; Lackey, C. A.; Long, C. J.; Miura, M.; Morris, J. E.; Murthy, N.; Nabeshima, Y.; Park, T. G.; Press, O. W.; Shimoboji, T.; Shoemaker, S.; Yang, H. J.; Monji, N.; Nowinski, R. C.; Cole, C. A.; Priest, J. H.; Harris, J. M.; Nakamae, K.; Nishino, T.; Miyata, T. J. Biomed. Mater. Res. 2000, 52, 577.
5. Kitayama, T.; Shibuya, W.; Katsukawa, K. Polym. J. 2002, 34, 405.
6. Ito, M.; Ishizone, T. Polym. Prep., Jpn. 2003, 52,146.
7. Isobe, Y.; Fujioka, D.; Habaue, S.; Okamoto, Y. J. Am. Chem. Soc. 2001, 123,

7180.

8. Hirano, T.; Higashi, K.; Seno, M.; Sato, T. J. Polym. Sci.:Part A: Polym. Chem. 2003, 41, 3463.
9. Yamada, K.; Nakano, T.; Okamoto, Y. Macromolecules 1998, 31, 7598
10. Zhang, J.; Liu, W.; Nakano, T.; Okamoto, Y. Polym. J. 2000, 32, 694.
11. Isobe, Y.; Yamada, K.; Nakano, T.; Okamoto, Y. J. Polym. Sci.:Part A: Polym. Chem. 2000, 38, 4693.
12. Gil, V. M. S.; Oliveira, N. C. J. Chem. Educ. 1990, 67, 473.
13. Macomber, R. S. J. Chem. Educ. 1992, 69, 375.
14. Wójcik, J.; Witanowski, M.; Stefaniak, L. Bull. Acad. Polon. Sci., Ser. Sci. Chim. 1978, 26, 927.