A New Chemoselective Anionic Polymerization Method for Poly(*N*-isopropylacrylamide) (PNIPAm) in Aqueous Media: Design and Application of Bulky Zincate Possessing Little Basicity

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Anionic polymerizations are among the most important methodologies in synthetic polymer chemistry.[1] Alkyllithiums[2] and Grignard reagents[3] have been widely used as powerful anionic initiators for prototypic anionic polymerizations such as that of styrene. Despite the synthetic potential of anionic polymerization, its use has been limited to less functionalized monomers. With highly functionalized monomers, undesirable side reactions, termination, and/or migration reactions can occur, because the initiators or the intermediary metal species are too reactive to coexist with various electrophilic functional groups such as carbonyl groups (amides, esters, etc.), and acidic hydrogen (NH, OH, etc.). In addition, the usual requirement of strict exclusion of moisture has limited the utility of the anionic polymerization method mediated by alkyllithiums and Grignard reagents, especially at the industrial level. Thus, a new and practical anionic polymerization method compatible with the functional group is highly desirable.

On the basis of soft nucleophilicity, high chemoselectivity, and controlling reactivity by the ligation environment, organozincates are very attractive candidates for highly selective anionic initiators.[4] We have previously clarified that the nucleophilicity,[5] basicity,[6] and halogen−metal exchange ability[7] of zincates can be tuned by the ligation environment. Herein, we present the newly designed dilithium tetra-*tert*-butylzincate (^{t}Bu$_4$ZnLi$_2$) possessing both high nucleophilicity for 1,4-addition to enone and little basicity and its practical applications as an initiator to chemoselective anionic polymerization of multifunctionalized monomers, such as *N*-isopropylacrylamide (NIPAm), *N*,*N*-dimethylacrylamide (DMA), acrylamide (AM), and 2-hydroxyethyl methacrylate (HEMA).

Poly(*N*-isopropylacrylamide) (PNIPAm, Scheme 1), exhibits unique temperature-sensitive properties.[8] It has been applied in various ways in organic chemistry,[9] biotechnology,[10] and material sciences.[11] However, since the multifunctionalized monomer, NIPAm, possesses an acidic amide−NH hydrogen and a conjugated carbonyl moiety, which provides a 1,2-addition site in addition to the desired 3,4-addition site, the polymerization of unprotected NIPAm has been reported only by a radical mechanism.[12] From the viewpoint of flexibility and applicability for further functionalization of PNIPAm, the development of chemoselective anionic polymerization would be extremely useful.

Table 1. Anionic Polymerization of NIPAm Initiated by Zincates[a]

run	initiator	[monomer]$_0$/ [initiator]$_0$	solvent	time (h)	yield (%)[b]	M_n[c]	M_w/ M_n[c]
1	Me$_3$ZnLi	50	THF	24	0		
2	Me$_4$ZnLi$_2$	50	THF	24	0		
3	^{t}Bu$_4$ZnLi$_2$	50	THF	24	8	7000	1.50
4	^{t}Bu$_4$ZnLi$_2$	50	THF	1 week	33	7000	2.17
5	^{t}BuLi	50	THF	24	0		
6	^{t}Bu$_4$ZnLi$_2$	50	MeOH	24	76	18 000	1.65
7	^{t}Bu$_4$ZnLi$_2$	50	H$_2$O	3	92	27 000	2.72
8	^{t}Bu$_4$ZnLi$_2$	25	H$_2$O	3	86	17 000	2.85
9	^{t}Bu$_4$ZnLi$_2$	12.5	H$_2$O	3	72	7000	2.71

[a] The reaction conditions: $[\mathrm{NIPAM}]^0 = 0.5$ M; $[\mathrm{Zn}] = 10$ mM, at room temperature. [b] Hot water insoluble part. [c] Determined by GPC based on polystyrene standards using DMF as a solvent.

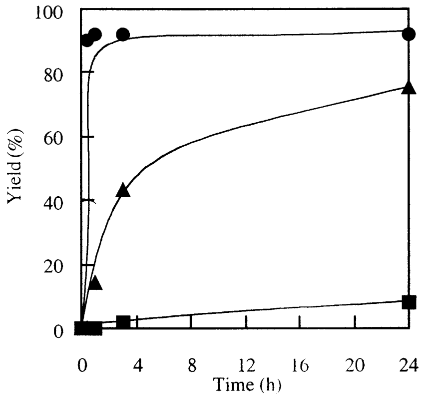

Figure 1. Solvent effect on time−yield profiles in the polymerization of NIPAm. Water (filled circles), methanol (filled triangles), or THF (filled squares) as a solvent (0.5 M).

We first evaluated the ability of various zincates to promote chemoselective anionic polymerization using NIPAm as a monomer (Table 1). The polymerization reactions with the use of Me ligand zincates, Me$_3$ZnLi,[5] or Me$_4$ZnLi$_2$,[7] as initiators did not proceed at all, but instead undesired reactions occurred. However, when a mixture of newly designed ^{t}Bu$_4$ZnLi$_2$, prepared in situ by mixing ^{t}Bu$_2$Zn and ^{t}BuLi (2 equiv),[13] and NIPAm (1:50 molar ratio) in THF was stirred at room temperature for 24 h, PNIPAm (**1**) was obtained, though in only 8% yield. Extension of the reaction time to 1 week gave **1** in 33% yield. Under the same reaction conditions, ^{t}BuLi itself did not promote this polymerization at all.

This new feature of the chemoselectivity of ^{t}Bu$_4$ZnLi$_2$, i.e., inertness to the acidic NH hydrogen, prompted us to examine further whether this system could be applied in protic solvents. To evaluate solvent effects more clearly, the time−yield profiles of the polymerization reaction of NIPAm were monitored in different solvents (Figure 1). In the polymerization of NIPAm using ^{t}Bu$_4$ZnLi$_2$, the nature of the solvent dramatically influenced the yield and the polymerization rate. When a protic polar solvent such as MeOH or H$_2$O was used, the polymerization reaction was drastically accelerated as compared with that in an aprotic, less polar solvent, THF. In H$_2$O, the yield was increased and reached the maximum (92%), within 15 min. The finding that a polar

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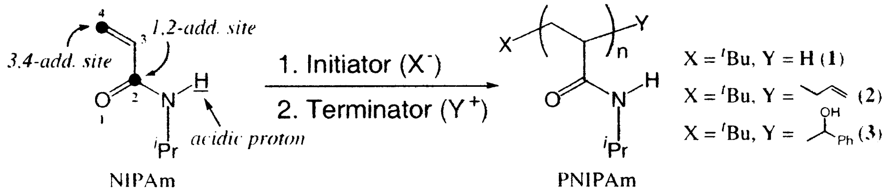
Scheme 1



solvent accelerated the polymerization reaction is characteristic of *ionic* polymerization. On the other hand, no polymerization reaction took place with ^{t}BuLi, $ZnCl_2$, LiCl, or LiOH. This rules out the promotion of this polymerization by these species.

We next measured the lower critical solution temperature (LCST),[14] ^{1}H NMR, and ESI−MS spectra of the obtained PNIPAm (**1**) in order to obtain structural information. LCST was around 31 °C which is consistent with previous data.[8] The ^{1}H NMR spectrum of the obtained **1** showed that the integration of N−H proton area is the same as that of methyne proton of the ^{i}Pr group, indicating that no chain transfer polymerization had occurred. The ESI−MS spectrum of the obtained **1** revealed that a single *tert*-butyl group existed in each polymer chain, and the difference of the individual peaks corresponded to the weight of the monomer (NIPAm; $M = 113$).[15] These spectra confirmed the polymer structure as ^{t}Bu−(NIPAm)$_n$−H (Figure 2a). The results strongly support the view that the present polymerization reaction using ^{t}Bu$_4$ZnLi$_2$ proceeds chemoselectively by successive 3,4-addition reactions.

The virtue of the present method is the ease of anionic end group transformations. After the initial polymerization of NIPAm using ^{t}Bu$_4$ZnLi$_2$, the resulting terminal zincate of the PNIPAm end can be trapped with an electrophile such as allyl iodide or benzaldehyde to give end-modified new polymers, **2** and **3**, respectively. The end group modifications were confirmed by the ESI−MS spectra of the obtained polymers **2** and **3**, which could be attributed to ^{t}Bu−(NIPAm)$_n$−allyl + Na$^+$ (Figure 2) and ^{t}Bu−(NIPAm)$_n$−CH(OH)Ph + Na$^+$ (Supporting Information), respectively.[15] The ^{1}H NMR spectra of **2** and **3** revealed 40% and 90% incorporation of the allyl or PhCH(OH) residue into the polymer end, respectively. These end group transformations would provide a good foundation for synthesis of further functionalized PNIPAm and related macromolecules. Finally, the generality of the present method was preliminarily examined. This anionic polymerization initiated by ^{t}Bu$_4$ZnLi$_2$ proved to be applicable for the polymerization of DMA, AM, and HEMA. These reactions gave the desired poly(DMA),[16] poly(AM),[17a] and poly(HEMA)[17b] in 74%, 84%, and 92% yields, respectively.

In summary, we have developed a new organozincate-mediated anionic polymerization using ^{t}Bu$_4$ZnLi$_2$ as an initiator. Several features of this new protocol are noteworthy. First, this anionic polymerization has high compatibility with protic solvents, which significantly accelerate the reactions. Therefore, this method is free from any requirement for the protection of acidic protons or strictly anhydrous reaction conditions. Second, the polymer growth was well-regulated, and the terminal zincate of the polymer end could be modified by electrophilic traps. Finally, this method possesses great versatility and high chemoselectivity, and multifunctionalized monomers, such as NIPAm, DMA, AN, and HEMA, could be polymerized in high yields. In the present organozincate-mediated anionic polymerization system, the reactivity and selectivity of zincates can be tuned via adjustment of several factors, such as the central metal, the type and number of ligands, and the type of countercations.[4−7] Therefore, this methodology

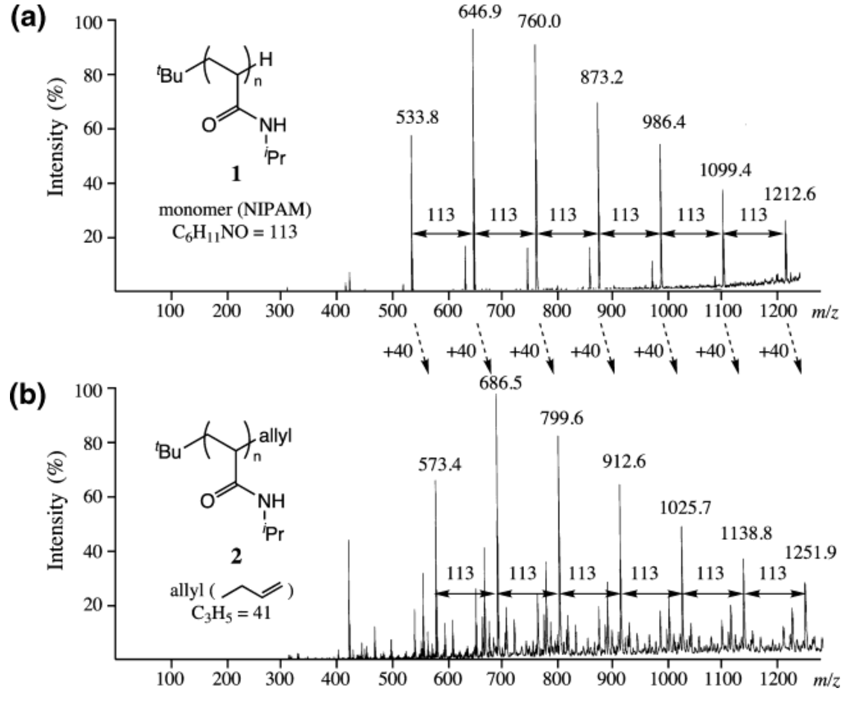


Figure 2. ESI−MS spectra of (a) ^{t}Bu−(NIPAm)$_n$−H and (b) the end-allylated poly(NIPAm).

should have a wide range of applications for highly functionalized macromolecules.

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Supporting Information Available: Text giving experimental procedures and characterizations, including a table of NMR data, a figure showing an ESI−MS spectrum, and figures showing NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For the measurement of ESI−MS spectra, the polymers of low molecular weight were synthesized by the control of the initial [monomer]/[initiator] ratio and these were used.

(16) $M_n = 35\,000$; $M_w/M_n = 2.02$ (determined by GPC).

(17) $M_n = 19\,000$. Determined by ^{1}H NMR. Due to the poor solubility of the product, molecular distribution could not be determined.

(18) $M_n = 7400$. Determined by ^{1}H NMR. Due to the poor solubility of the product, molecular distribution could not be determined.

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