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ARTICLE

The effect of Z-group modification on the RAFT polymerization of *N*-vinylpyrrolidone controlled by "switchable" *N*-pyridyl-functional dithiocarbamates

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The ability of a RAFT agent to control the polymerization of a monomer is dictated by the structures of both the monomer and the RAFT agent. In this paper, the polymerization of *N*-vinylpyrrolidone was examined with a series of cyanomethyl *N*-aryl-*N*-pyridyl dithiocarbamates [(4-R′Ph)N(py)C(=S)SCH$_2$CN] varying in the substituent (R′) at the 4-position on the phenyl ring. The polymerization of *N*-vinylpyrrolidone was best controlled when R′ was methoxy; one of the least active RAFT agents in the series. The preservation of RAFT agent functionality was demonstrated by chain extension experiments with further *N*-vinylpyrrolidone. Again best control again was found for the RAFT agent with R′=MeOPh. The utility of this RAFT agent was also proved with the preparation of poly(*N*-isopropylacrylamide)-*block*-poly(*N*-vinylpyrrolidone).

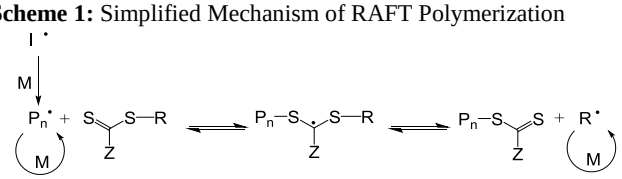
Introduction

Polymers of *N*-vinylpyrrolidone (NVP) are important due to their biocompatibility, good adhesion characteristics, resistance to hydrolysis in aqueous media and low toxicity.[1-5] NVP polymers are therefore often targeted for biomedical applications, which include soluble drug carriers, biodegradable networks for controlled drug delivery and viscosity modifiers for use in pharmaceutics and personal care products.[6, 7]

Various reversible-deactivation radical polymerization (RDRP) techniques have been applied in controlling NVP polymerization.[8‡] Atom transfer radical polymerization (ATRP)[9, 10] and nitroxide mediated polymerization (NMP),[11] have been shown to be ineffective in controlling the polymerization of NVP. On the other hand, reversible addition-fragmentation chain transfer (RAFT) polymerization[12-16] (Scheme 1) has been successfully used to overcome the problems associated with control of NVP polymerization to provide low dispersity, well characterized diblock[17], triblock, star and random copolymers.[18]

The success of a RAFT polymerization is crucially dependent on an appropriate pairing of the RAFT agent **1** with the monomer(s). The effectiveness (i.e., the ability to deliver polymers of targeted molar mass of low dispersity) of a RAFT agent in controlling a given polymerization can be rationalized in terms of the reactivity of the monomer and the homolyticleaving group ability of the propagating species formed upon radical addition. When the double bond is

Scheme 1: Simplified Mechanism of RAFT Polymerization



1 **2** **3**

conjugated to an unsaturated system such as a carbonyl, an aromatic ring or to a nitrile the monomer is referred to as a more active monomer (MAM). Examples are methyl methacrylate, styrene and acrylonitrile, respectively. Such monomers undergo facile reaction with radicals.[19] MAM-derived radicals are good homolytic leaving groups in large part due to this resonance stabilisation. The RAFT agents which are most effective in controlling the polymerization of MAMs are the more reactive dithioesters and trithiocarbonates where the connecting atom of Z is carbon or sulfur respectively.[20] Even when the intermediate **2** is highly stabilized, fragmentation of the intermediate is extremely facile.

Monomers with a double bond that bears a saturated carbon atom or is conjugated to a lone pair on oxygen or nitrogen (e.g., NVP) are usually less active monomers (LAMs). Polymerization of these monomers generates propagating radicals which are poor homolytic leaving groups. Thus, polymerization of LAMs is best controlled with dithiocarbamates or xanthates where the connecting atom of Z is nitrogen or oxygen. For these systems the macro-RAFT

intermediate **2** has reduced stability. If a more active RAFT agent is used (i.e., one with a higher rate of chain transfer) strong retardation or inhibition is frequently observed. Thus the use of dithiobenzoates and trithiocarbonates in attempts to control NVP polymerization has met with limited success.[11, 21-23]

The high reactivity of NVP derived propagating radicals also leads to deleterious reactions during polymerization such as head addition and chain transfer to monomer or polymer.[6, 24] The contribution of these reactions becomes more prevalent with increasing monomer conversion. The matter is further complicated by the presence of unwanted side reactions that can be catalyzed by impurities[25] such as dimerization, hydration and hydrolysis as well as the tendency for the monomer to participate in electron transfer reactions leading to reactive radical cation species in the presence of a sufficiently electrophilic acceptor.[26]

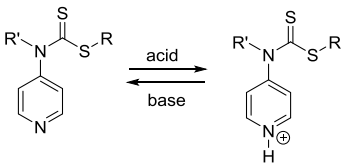
Dithiocarbamates[23, 27, 28] and xanthates[29-31] have been used with success in RAFT-mediated polymerization of NVP providing low dispersity, well controlled PNVP.[30] While xanthates (and typical dithiocarbamates) can deliver control over NVP polymerization, these RAFT agents are typically poor at controlling the polymerization of MAMs. This can be attributed to their inherently lower reactivity.[32]

A new class of "switchable" *N*-methyl-*N*-4-pyridinyldithiocarbamate RAFT agents such as **4** (see Scheme 2) have been developed.[33] These RAFT agents have the ability to control the polymerization of both MAMs and LAMs, providing a means for the straightforward synthesis of block copolymers incorporating both monomer classes (*i.e.*, polyMAM-*block*-polyLAM).[33-35] It must be noted however that for the preparation of block copolymers, these RAFT agents are still limited by the order in which monomer units are introduced, as they are with conventional RAFT methods.[§] To ensure rapid consumption of macro-RAFT agent and efficient chain extension, the monomer that gives the more stabilised propagating radicals must be introduced first (i.e., methacrylates/methacrylamides prior to styrenes/ acrylates/acrylamides prior to vinylamides/vinyl esters; MAMs before LAMs).[32] When using a "switchable" RAFT protocol the MAM block must be prepared first due to the poor homolytic leaving group ability of polyLAM derived radicals.[33]

The reactivity of these "switchable" RAFT agents is modulated by using an appropriate acid or base to switch between the activated pyridinium form **4**-**H**$^+$, suitable for control of the polymerization of MAMs, and the deactivated pyridine form **4**, suitable for the polymerization of LAMs (Scheme 2).

More recently we reported polymerizations with *N*-aryl-*N*-4-pyridinyldithiocarbamates.[36] These RAFT agents are both more effective with MAMs in their protonated pyridinium form and more effective with LAMs in their neutral pyridine form. We showed that the activity of RAFT agents (i.e. rate of chain transfer) could be modulated by incorporation of an aryl groups providing differing electron demand (**4**-**9**).[36]

Scheme 2: Acid/base switchable RAFT agents **4-9** (R = CH_2CN)



4-9 **4-H$^+$-9-H$^+$**

RAFT agent	R′
4	Me
5	4-MeOPh
6	Ph
7	4-FPh
8	4-pyridyl
9	4-NCPh

increasing activity

Through calculation of the apparent chain transfer coefficients (C_{tr}^{app}) in methyl acrylate, *N*-vinylcarbazole and vinyl acetate polymerization we were able to correlate increased activity with decreased thiocarbonyl electron density. The RAFT agents bearing the strongest electron-withdrawing moieties on Z possess the highest activity (see Scheme 2). All the *N*-aryl functional RAFT agents **5**-**9** performed better than the *N*-methyl functional dithiocarbamate **4** as control agents in the polymerization of the MAM methyl acrylate (MA). In this study the cyanomethyl R group was used exclusively due to its ability to effectively reinitiate the polymerization of both MAMs and LAMs.[36]

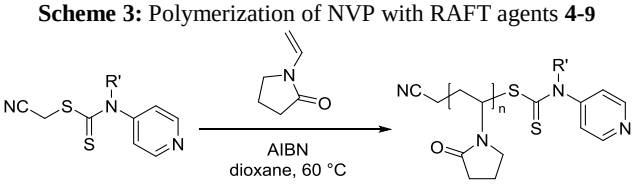
In this work we extend the previous study by investigating the effectiveness of this same series of switchable RAFT agents in controlling the polymerization of NVP. The RAFT agents were assessed based on their ability to control molar mass and dispersity. The most effective RAFT agents were further assessed by preparation of diblocks based on NVP. In turn, the RAFT agent that gave the best results in NVP polymerization was used in the preparation of poly(*N*-isopropylacrylamide-*block*-NVP) to assess its suitability for the synthesis of NVP containing poly(MAM)-*block*-poly(LAM) block copolymers.

Results and Discussion

Polymerization of NVP using different RAFT agents

In this study PNVP homopolymers were synthesized with target molar mass of 22200 g mol^{-1} (*DP* = 200) using six cyanomethyl RAFT agents (**4**-**9**) varying only in the R′ substituent (see Scheme 3). Experimental results are given in
Table 1. Note that the experimental M_n is obtained through conventional calibration with low dispersity polystyrene standards and given in polystyrene equivalents.

Scheme 3: Polymerization of NVP with RAFT agents **4-9**



4-9 **PNVP-4-9**

The linear pseudo-first order kinetic plot (Figure 1) demonstrates that RAFT agents **4**-**7** cause no inhibition from slow reinitiation or slow fragmentation in the polymerization of NVP. The results obtained with these RAFT agents **4**-**7** (

Table 1) display a characteristic decrease in dispersity to moderate conversion (~50 %), due to chain length equilibration following RAFT pre-equilibrium. As expected for the polymerization of LAMs such as NVP, higher conversion leads to increased dispersity due to increased prevalence of processes such as termination and irreversible chain transfer. Plots illustrating the evolution of M_n and $Đ$ with monomer conversion can be found in the supporting information as Figure S1 and S2 respectively.

The methyl RAFT agent **4** gave good control over molar mass but exhibited only moderate dispersity control at low conversion (Entry 1, Table 2; $Đ$ = 1.45, 27 % conversion) and at very high conversion (Entry 5, Table 2; $Đ$ = 1.5, 93 % conversion). The methoxyphenyl RAFT agent **5** displayed excellent control of molar mass and gave lowered dispersity even at high conversion (Entry 10, Table 2; $Đ$ = 1.36, 94 % conversion). The phenyl RAFT agent **6** also exhibited good control over molar mass with monomer conversion with low dispersity obtained at low conversion (Entry 11, Table 2; $Đ$ = 1.10, 36 % conversion). However, at high conversion **6** delivered higher dispersity polymers (Entry 15, Table 2; $Đ$ = 1.55, 95 % conversion). The polymerization of NVP in the presence of the fluorophenyl RAFT agent **7** exhibited linear pseudo-first order kinetics but gave polymers of relatively high dispersity at high conversion, most likely due to increased activity of the RAFT agent promoting deleterious side reactions (Entry 20, Table 2; $Đ$ = 1.89, 97 % conversion).

RAFT agents **8** and **9** were ineffective in controlling the polymerization of NVP due to their high activity. The polymerization of NVP using the pyridyl substituted RAFT agent **8** displayed an inhibition period of 17 h (see Figure 1) after which rapid, uncontrolled polymerization occurred (Entry 25, Table 2; $Đ$ = 3.09, 87 % conversion). The cyanophenyl-

Table 1: Details of NVP polymerization reactions with RAFT agents **4-9**[a]

Entry	RAFT Agent	R′	Time (h)	M_n[b]	M_n calc.[c] (g mol^{-1})	$Đ$[b]	Conv. %.
1	**4**	Me	3	3140	5970	1.45	27
2			5	6390	9590	1.23	43
3			10	9450	15100	1.19	68
4			17	12100	21000	1.30	94
5			25	12200	21000	1.50	93
6	**5**	4-MeOPh	3	3680	6980	1.20	31
7			5	6640	11200	1.11	50
8			10	12700	16400	1.20	74
9			17	13800	17300	124	78
10			25	18900	20900	1.36	94
11	**6**	Ph	3	6970	8100	1.10	36
12			5	9960	9860	1.13	44
13			10	11700	16800	1.20	76
14			17	13200	18400	1.30	83
15			25	14400	21000	1.55	95
16	**7**	4-FPh	3	7260	12300	1.16	56
17			5	8290	14000	1.13	63
18			10	10900	16200	1.34	73
19			17	13400	20000	1.47	90
20			25	15800	21500	1.89	97
21	**8**	4-pyridyl	3	1080	oligomer	N/A	5
22			5	1120	oligomer	N/A	9
23			10	1510	2290	2.55	10
24			17	2700	7840	3.55	35
25			25	37000	20000	3.09	87
26	**9**	4-cyanophenyl	25		No reaction		

[a]Target molar mass 22,000 g mol^{-1} (DP=200); [NVP] = 6.00 M, [RAFT] = 3.0 × 10^{-2} M, [AIBN] = 7.5× 10^{-3} M in 1,4-dioxane, T = 60 °C, [b] in polystyrene equivalents from GPC with DMF eluent, T = 80°C, LiCl = [50 mM] . [c]M_n(calc)= $([M]_0 - [M]_t])/([RAFT]_0 \times MW_{monomer} \times$ % conv. + $MW_{RAFT\ AGENT}$

functional RAFT agent **9** completely inhibited the polymerization NVP over 25 h (Entry 26, Table 2), and is therefore omitted from Figures 1, S1 and S2. The more active dithiocarbamates possess activity similar to those of trthiocabonates.[36, 37] These observations are thus consistent with that reported by Postma *et al*[28] in attempting to control NVP polymerization with a phthalimidomethyl trithiocarbonate RAFT agent. In these cases the RAFT agent may be sufficiently electrophilic to undergo electron transfer reaction directly with the NVP monomer,[26] resulting in RAFT agent consumption and loss of control.

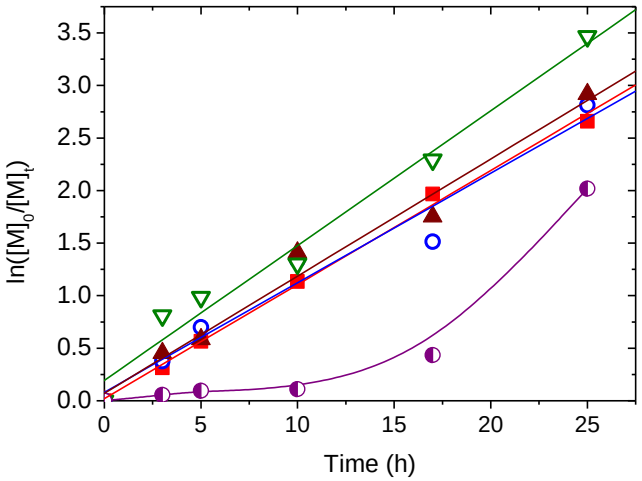
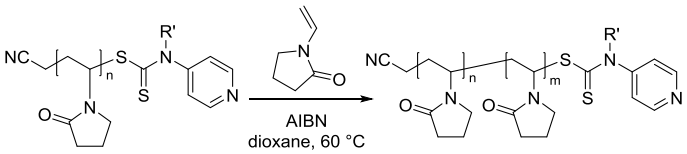


Figure 1: Pseudo-first order kinetics plots for the RAFT polymerization of NVP in the presence of RAFT agents **4** (■), **5** (○), **6** (▲), **7** (▽) and **8** (◐).

In summary the methoxyphenyl RAFT agent **5** delivers the optimal results for NVP polymerization due its precisely balanced activity. Increased activity in comparison to **4** allows for faster RAFT agent consumption, resulting in lower dispersity polymers from rapid completion of the RAFT pre-equilibrium. Decreased activity compared to **6-9** limits the prevalence of side reactions such as those described above being encountered during polymerization, which again results in superior materials.

Chain Extension of poly(*N*-vinylpyrrolidone) macro-RAFT agents with *N*-Vinylpyrrolidone

In order to probe the retention of the RAFT end-group following NVP polymerization, chain extension experiments were performed using the two best performing RAFT agents; **4** and **5** (Scheme 4). In RAFT polymerization chain extension with the same monomer eliminates any complicating kinetic factors such as non-ideal partitioning of the RAFT intermediate **2** or inefficient reinitiation by the macro-RAFT agent derived radical, as P_n = R. The chain extended polymers were prepared using the same reaction conditions discussed in the section above. Following purification via precipitation the isolated PNVP samples were chain extended with further NVP.



Scheme 4: Chain extension of PNVP-**4** (R′= Me) and PNVP-**5** (R′= 4-MeOPh) macro-RAFT agents with NVP.

Figure 2 and Table 2 show the results of the chain extension experiments. Both RAFT agents provide good control over the polymerization of NVP. However, the methoxyphenyl macro-RAFT agent PNVP-**5** delivers a chain extended polymer of lower dispersity ($Đ$ = 1.24) than does the methyl macro-RAFT agent PNVP-**4** ($Đ$ = 1.39). As with the previous observations, chain extension experiments were best controlled with the methoxyphenyl RAFT agent **5**. At full conversion of NVP bimolecular termination is observed as a shoulder in the molar mass distribution for chain extension of both PNVP-**4** and PNVP-**5** (see red traces in Figure 2 (a) and (b)). This is more clearly observed in PNVP-**5**, due to the lower dispersity of the main population.

The dispersity is higher in some cases than in the original kinetic experiments (i.e.
Table 1, entry 3; $Đ$ = 1.19 compared to Table 3, Entry 1; $Đ$ =1.24) as the macro-RAFT

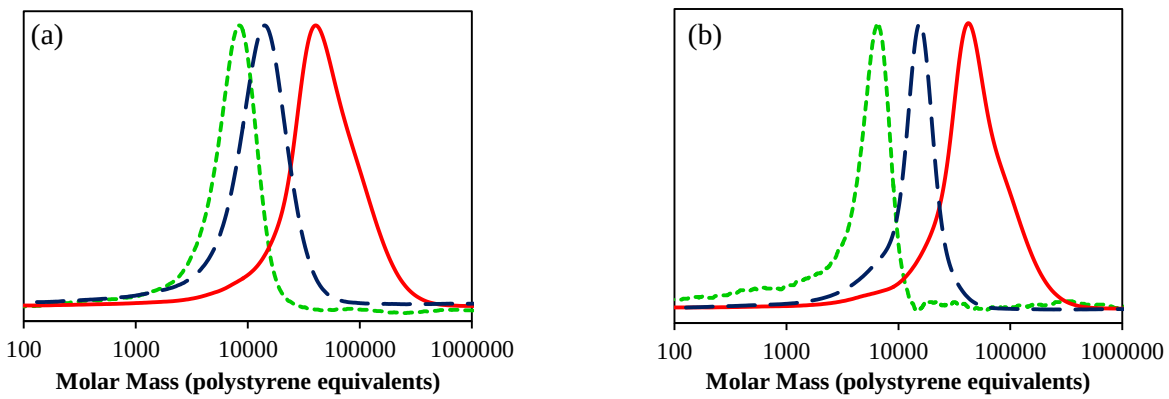


Figure 2: GPC chromatograms of (a) PNVP-A-**4** (- - -), PNVP-A-PNVP-4h-**4** (– – –), PNVP-A-PNVP-10h-**4** (—) and (b) PNVP-B-**5** (- - -), PNVP-B-PNVP-4h-**5** (– – –), PNVP-B-PNVP-10h-**5** (—).

Table 2: Chain extension of macro-RAFT agents PNVP-**4** (R′ = Me) and PNVP-**5** (R′= 4-MeOPh) with NVP.

Entry	Polymer	M_n [c]	M_n(calc.)[d] (g mol^{-1})	$Đ$[c]	Time (h)	Conv. %
1	PNVP-A-**4**[a]	6950	7980	1.24	4	45
2	PNVP-A-PNVP-4h-**4**[b]	11000	14700	1.39	4	41
3	PNVP-A-PNVP-10h-**4**[b]	23200	27800	2.00	10	100
4	PNVP-B-**5**[a]	5560	7090	1.15	4	40
5	PNVP-B-PNVP-4h-**5**[b]	12400	15100	1.24	4	43
6	PNVP-B-PNVP-10h-**5**[b]	24900	27800	1.81	10	100

[a][NVP]:[RAFT]:[AIBN]=160:1:0.3; [b][NVP]:[RAFT]:[AIBN] =200:1:0.25 in 1,4-dioxane, T = 60 °C; [c]in polystyrene equivalents from GPC with DMF eluent, T = 80 °C, LiCl = [50 mM]; [d]M_n(calc)= ([M]$_0$ – [M]$_t$])/([RAFT]$_0$ × MW$_{monomer}$ + MW$_{RAFT\ Agent}$

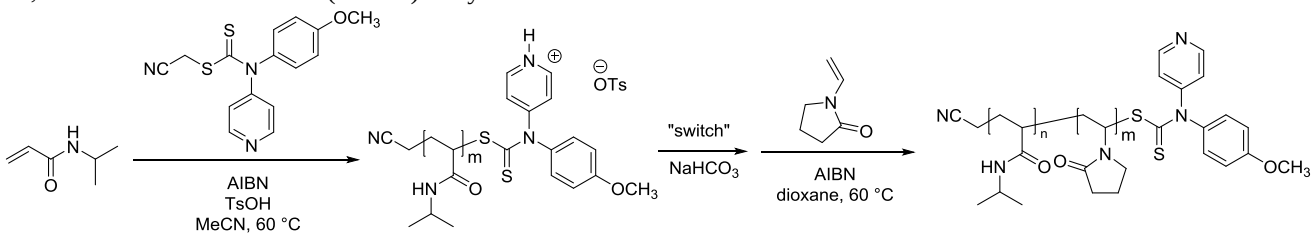
agent was isolated after shorter reaction time to ensure high end-group functionality. As radical polymerization is never completely free from irreversible termination[32] a relationship between the amount of decomposed initiator and retention end group fidelity exists; for every initiator derived radical that initiates polymerization there is another that terminates a chain. Typically, as a RAFT polymerization reaches higher conversion loss of end group functionality is observed. For the formation of block copolymers it is particularly important that end group fidelity is as high as possible to ensure optimal chain extension of the first block.

Block Copolymer Synthesis

Poly(*N*-isopropylacrylamide)-*block*-poly(*N*-vinylpyrrolidone)

The utility of a switchable RAFT agent lies in the ability to produce block copolymers incorporating monomer combinations previously inaccessible through conventional RDRP techniques. For the RAFT agents considered in this work, more active monomers (MAMs) may be controlled through the protonation of the pyridine ring activating the thiocarbonyl group towards radical addition. Herein we utilise *N*-isopropylacrylamide (NIPAM) as an example MAM to demonstrate the synthesis of block copolymers of this type. NIPAM is a more active monomer owing to its vinyl group being conjugated to the amide carbonyl. NIPAM based polymers have become of increasing of interest due to a lower critical solution temperature (LCST) in aqueous solution close to body temperature (~32 °C)[38] allowing for a range of applications including drug delivery[39-41] and bioconjugated polymer therapeutics.[42-44]

NIPAM was polymerized in the presence of the methoxyphenyl **5** as this RAFT agent delivers the best control over NVP polymerization (an experiment for the synthesis of PNIPAM using the methyl RAFT agent **4** can be found in the Supporting Information) The resulting polymer was low dispersity PNIPAM-**5** (Table 3, Entry 1). Chain extension of PNIPAM-**5** with NVP gave the desired block



Scheme 5: Synthesis of PNIPAM-*block*-PNVP under the control of RAFT agent **5** (R′= 4-MeOPh)

Table 3: Synthesis of PNIPAM-*block*-PNVP Using RAFT agent **5** (R′ = MeOPh)

Entry	Polymer	M_n[c]	M_n (calc.)[d] (g mol^{-1})	$Đ$[c]	Time (h)	Conv. %
1	PNIPAM-**5**[a]	17300	16900	1.06	3	69
2	PNIPAM-*bl*-PNVP-**5**[b]	22500	24900	1.15	4	48

[a][NIPAM]:[RAFT]:[AIBN] = 216:1:0.4 in 1,4-dioxane, T = 60 °C; [b] [NVP]:[RAFT]:[AIBN] = 220:1:0.3 in 1,4-dioxane, T = 60 °C; [c]in polystyrene equivalents from GPC with DMF eluent; T = 80 °C, LiCl = [50 mM]; [d] M_n(calc)= ([M]$_0$ – [M]$_t$])/([RAFT]$_0$ × MW$_{monomer}$ + MW$_{RAFT\ AGENT}$

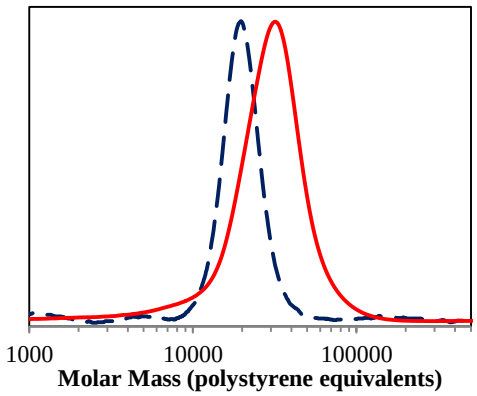


Figure 3: GPC chromatograms of PNIPAM-**5** (– – –) and PNIPAM-*b*-PNVP-**5** (—)

copolymer PNIPAM-*b*-PNVP-**5** with low dispersity (Figure 3).

RAFT syntheses of block copolymers of NVP and NIPAM have been previously reported using xanthates as the control agent.[45-48] Xanthates have lower activity than protonated pyridinium RAFT agents such as **5** and thus give PNIPAM of higher dispersity for comparative M_n (ca. ~1.3 for M_n = 18000-22000 g mol^{-1}).[49] Furthermore these syntheses are not ideal as the PNVP block (the poorer homolytic leaving group) was prepared prior to the NIPAM block, leading to poor chain extension efficiency. We therefore suggest the use of 'switchable' RAFT agents as a superior method for the preparation of low dispersity NIPAM/NVP based block copolymer materials of high purity.

Conclusions

Through polymerizing NVP in the presence of a series of *N*-aryl-*N*-pyridyl dithiocarbamate RAFT agents with varying substituents on the 4-position of the aryl ring, we have demonstrated that structural effects change the reactivity of the RAFT agent significantly affect the control of the polymerization of NVP.

The polymerization of NVP was followed with a series of six RAFT agents **4**-**9** (**4** R′ = methyl, **5** R′ = 4-methoxyphenyl, **6** R′ = phenyl, **7** R′ = 4-fluorophenyl, **8** R′ = 4-pyridyl, **9** R′ = 4-cyanophenyl). The less active RAFT agents were found to give excellent (**4** and **5**) to moderate control (**6** and **7**). The polymerization of NVP was uncontrolled by **8** and **9** due to the high activity of the RAFT agents which inhibit the polymerization (as seen with **9**). Of all RAFT agents the methoxyphenyl **5** delivered the best control over the polymerization of NVP, demonstrating that a considerable difference between the ability of the two less active RAFT agents exist. This was further demonstrated through the chain extension of a PNVP macro-RAFT agent with NVP. In this case **5** gave a superior polymer with significantly lower dispersity than **4**. To demonstrate the utility switchable RAFT agents a PNIPAM-*block*-PNVP was block copolymer was prepared using RAFT agent **5**, through use of an acid/base switching protocol.

Experimental

Materials. All solvents were of analytical grade unless otherwise stated. 4-Aminopyridine, bromoacetonitrile, carbon disulfide (CS_2), *N*,*N*-diisopropylethylamine, ethyl choroformate, *N*-isopropylacrylamide (NIPAM), lithium aluminium hydride and 1-vinylpyrrolidin-2-one, (*N*-vinylpyrrolidone, NVP) were purchased from Sigma-Aldrich. *p*-Toluenesulfonic acid monohydrate (TsOH) was purchased from Merck. 2,2′-azobis(2-methylpropanenitrile) (α,α'-azobis(isobutyronitrile), AIBN) was purchased from Acros and purified via recrystallization from methanol before use. NVP was filtered through neutral alumina and purified by fractional thawing of frozen sample (zone refining)[50] immediately before use. NIPAM was used as received. All deuterated solvents were obtained from Cambridge Isotope Laboratories.

Characterisation. Nuclear Magnetic resonance (NMR) spectra for structural assignments and monomer conversion were obtained on a Bruker Avance 300 MHz spectrometer. All NMR spectra were internal referenced to residual solvent.[51] Gel Permeation Chromatography (GPC) was performed on a system comprising a Waters 590 HPLC pump and a Waters 410 refractive index detector equipped with 3 × Waters Styragel columns (HT2, HT3, HT4, each 300 mm × 7.8 mm providing an effective molecular weight range of 100-600000). The eluent was *N*,*N*-dimethylformamide (DMF) containing 2.1 g L^{-1} of LiCl at 80 °C (flow rate: 1 mL min^{-1}). Number-average (M_n) and weight-average (M_w) molecular weights were evaluated using Waters Empower software. The GPC columns were calibrated with low dispersity polystyrene standards (Polymer Laboratories) ranging from 3100 to 650000 g mol^{-1} and molecular weights are reported as polystyrene equivalents. A third order polynomial was used to fit the log M_p vs. time calibration curve, which was linear across the molecular weight ranges.

RAFT Agent Synthesis. The cyanomethyl *N*-aryl-*N*-pyridyl dithiocarbamates were prepared by the previously reported procedures[36] except for cyanomethyl methyl(pyridin-4-yl)carbamodithioate **4**, adapted from previous literature reports[33, 52-54] which is detailed below.

Synthesis of Ethyl Pyridin-4-ylcarbamate.

A solution of 4-aminopyridine (10.0 g, 106 mmol) in CH_2Cl_2 was prepared at 0 °C. To the solution *N*,*N*-diisopropylethylamine (13.7 g, 106 mmol) and ethyl choroformate (10.1 mL, 106 mmol) were added. The solution was stirred overnight at room temperature and volatiles were removed *in vacuo*. To the solid a concentrated saturated solution of aqueous $NaHCO_3$ was added and stirred for 3 h, concentrated and then dried under vacuum. The crude solid was then stirred in hot methanol (250 mL) for 1 h, filtered and the filtrate concentrated. The crude carbamate was then recrystallized from toluene/hexane to give 12.21 g (69 % yield) of the pure ethyl carbamate. ^{1}H NMR (300 MH$_Z$ $CDCl_3$) 8.42 (d, 2H, Ar*H*); 7.56 (d, 2H, Ar*H*); 4.28 (q, 2H, OCH_2); 1.31 (t, 3H, CH_3). ^{13}C NMR (75 MHz $CDCl_3$) 154.9 (*C*=O); 149.1 (Ar*C*); 148.6 (Ar*C*); 112.4 (Ar*C*); 62.3 (OCH_2); 15.1 (CH_3). This data is consistent with Smith *et al*.[53]

Synthesis of 4-(methylamino)pyridine.

To a 0 °C solution of *N*-(4-pyridyl) ethyl carbamate (8.6 g, 51 mmol) in dried THF (250 mL) was added lithium aluminium hydride (10.21 g, 269 mmol) over 1 h. The mixture was refluxed for 6 h and re-cooled to 0 °C, quenched sequentially

with water (15.0 mL), 20 % NaOH (8.0 mL) and water (50.0 mL). The suspension was passed through a pad of Celite and evaporation of the volatiles gave 4.61 g (82 % yield) of the crude product. ^{1}H NMR (300 MH$_Z$) 8.26 (d, 2H, Ar*H*); 6.42 (d, 2H, Ar*H*); 2.86 (d, 3H, C*H*$_3$). ^{13}C NMR (75 MHz CDCl$_3$) 154.2 (Ar*C*); 149.8 (Ar*C*); 107.2 (Ar*C*); 29.3 (*C*H$_3$). These data are consistent with Jiao *et al*.[55]

Synthesis of cyanomethyl methyl(pyridine-4-yl)carbamodithioate (4).

Potassium *tert*-butoxide (2.85g, 25.4 mmol) was added to a solution of 4-(methylamino)pyridine (2.75 g, 25.4 mmol) in dry THF (120 mL). The reaction mixture was left to stir at room temperature for 2 h after which CS_2 (3.36 mL, 56 mmol, 2.2 equiv) was added drop wise and the solution turned from a pale yellow to a dark bright yellow suspension. After the reaction was stirred at RT for 24 h bromoacetonitrile (2.0 mL, 28 mmol) was added. The solution was then stirred for an additional 3 h. Saturated $NaHCO_3$ (150 mL) was added and the solution was extracted with DCM (3 × 100 mL), washed with sat'd $NaHCO_3$ (3 ×100 mL) and water (2 × 100 mL). The organic phases were combined, dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. A light brown solid (3.4 g, 59 % yield) was afforded after purification through column chromatography (neutral Al_2O_3 Brockmann Activity III; eluent 50 % EtOAc/50 % *n*-heptane) and recrystallization in ethanol. ^{1}H NMR (300 MHz CDCl$_3$) δ 3.98 (s, 3H, NC*H*$_3$); 4.12 (s, 2H, SC*H*$_2$CN); 7.20 (m, 2H, Ar*H*); 8.05 (m, 2H, Ar*H*). These data agree with Benaglia *et al*.[33]

RAFT polymerization.

***Polymerization of N-Vinylpyrrolidone*.** The polymerization of NVP in the presence of RAFT agent **4** is given below. The polymerization of NVP using RAFT agents **5**-**9** is given in the supporting information.

***Synthesis of Poly(N-Vinylpyrrolidone) using Cyanomethyl methyl(pyridine-4-yl)carbamodithioate (4) at 60 °C*.**

The reaction solution was prepared with the dissolution of the RAFT agent **4** (33.5 mg, 0.15 mmol) in a 5 mL volumetric flask followed with the addition of NVP (3.33 g, 30.0 mol) and AIBN (6.1 mg, 0.038 mmol). The solution was then transferred into a Schlenk tube and degassed by sparging with N_2 in an ice bath. The solution was heated in an oil bath at 60 °C. The reaction was quenched via exposure to air and rapid chilling. The PNVP-**4** macro-RAFT agent was isolated via three cycles of precipitation into ether.

Chain extension of PNVP macro-RAFT agent with NVP.

The general procedure for chain extension is given below using macro-RAFT PNVP-**4**. For the synthesis using macro-RAFT PNVP-**5** consult the supporting information. Into a 5 mL standard volumetric flask were placed PNVP-**4** macro-RAFT (0.851 g, 0.15 mmol) and NVP (3.4 g, 30.5 mmol). AIBN (6.2 mg, 3.7 × 10^{-2} mmol) was added and the solution was made up to the mark with 1,4-dioxane The solution was transferred into a Schlenk tube and degassed via sparging with N_2 for 15 min in an ice bath. The reaction was then heated at 60 °C. Upon removal from the oil bath the reaction was quenched with exposure to air and rapid cooling in ice. The chain extended polymer was isolated via three cycles of precipitation into an 8-fold volume of diethyl ether and isolated by filtration.

Preparation of block copolymers through Switchable RAFT.

Synthesis of PNIPAM macro-RAFT agent.

A solution was formed with the addition of RAFT agent **6** (45.4 mg, 1.5 × 10^{-1} mmol) and TsOH (30.1 mg, 1.5 x 10^{-1} mol) into a small amount of MeCN in a 5 mL volumetric flask. NIPAM (3.5 g, 30.9 mmol) was added, followed with the addition of AIBN (8.6 mg, 5.3 × 10^{-2} mmol) and then the solution was made up to the mark with MeCN. The reaction was degassed via sparging with N_2 for 15 min with while cooling in ice. The reaction was heated for 3 h at 60 °C before it was exposed to oxygen and cooled. The reaction medium containing the PNIPAM-**5** macro-RAFT agent was passed through a column of sodium bicarbonate to deprotonate the RAFT chain-end and further purified by three cycles of precipitation into ether and isolated via filtration.

Synthesis of PNIPAM-block-PNVP

A solution of PNIPAM-**6** macro-RAFT agent (1.0 g, 5.9 × 10^{-2} mmol), NVP (1.05 g, 9.4 mmol), AIBN (2.9 mg, 1.7 × 10^{-2} mmol) and 1,4-dioxane to a volume of 2.5 mL was prepared in a volumetric flask. The solution was transferred into a Schlenk tube and degassed for 15 min in an icebath by sparging with N_2. The reaction was heated for 3 h at 60 °C before it was exposed to oxygen and cooled. Purification was achieved by three cycles of precipitation into ether followed by isolation by filtration.

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‡ IUPAC recommendations indicate that the term "living polymerization" be reserved for polymerization processes free from irreversible chain termination or irreversible chain transfer. As such the IUPAC recommended term reversible-deactivation radical polymerization is used in this manuscript when referring to radical polymerization processes where the effect of these processes is minimized.

§ The constraint of block order is also a limitation of other RDRP methods and not solely limited to RAFT based syntheses. Examples where the polymer that gives the less stablilized homolytic leaving group is prepared first do appear in the literature, however these examples are often performed for practical reasons and cannot be considered ideal.

†Electronic Supplementary Information (ESI) available: [Additional experimental conditions for polymer syntheses, plots of evolution of

molar mass (Figure S1) and dispersity (Figure S2) with monomer conversion and ^{1}H NMR spectra of macro-RAFT agents (Figures S3, S4 and S5)].
See DOI: 10.1039/b000000x/

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The effect of Z-group modification on the RAFT polymerization of *N*-vinylpyrrolidone controlled by "switchable" *N*-pyridyl-functional dithiocarbamates

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