

Supporting information for:

Improved Control Through a Semi-Batch Process in RAFT-Mediated Polymerization Utilizing Relatively Poor Leaving Groups.

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Experimental

Materials and methods

N-Vinylpyrrolidone (NVP) was purchased from Merck and vacuum distilled over 5% ground potassium hydroxide before use. Styrene and methyl methacrylate were obtained from Sigma Aldrich and were passed through a basic alumina column to remove inhibitor immediately before use. Potassium *O*-ethylthiocarbonate, anhydrous calcium chloride, anhydrous magnesium sulfate, potassium hydroxide pellets and anhydrous calcium sulfate were purchased from Merck and used as received. *N*-(Bromomethyl)phthalimide, bromobenzene, *N*-methylaniline, methyl 2-bromopropionate, bromoacetic acid, carbon disulfide, sodium hydride (60 % dispersion in mineral oil), 1,1-azobis(cyclohexanecarbonitrile) (V-88), and chloroform-*d* 99.8 atom % were purchased from Sigma Aldrich and used as received. Azobisisobutyronitrile (AIBN) was purchased from Merck and recrystallized from methanol before use. Benzene-*d*6 (99.6 atom %) was purchased from ACROS Organics and used as received. Methanol, chloroform, dichloromethane, 1,4-dioxane and diethyl ether were purchased from KIMIX. Methanol was fractionally distilled before use. Chloroform and dichloromethane were washed with concentrated sulfuric acid followed by 5% sodium bicarbonate solution and finally water before being dried over anhydrous calcium chloride and fractionally distilled from anhydrous calcium sulfate. Diethyl ether and 1,4-dioxane were distilled from sodium-benzophenone ketyl. Dimethylacetamide (Chromosolv® Plus, for HPLC ≥ 99.9%) was purchased from Sigma Aldrich and used as received. Butylated hydroxytoluene (BHT) 99% (GC) was purchased from Sigma Aldrich and used as received. Lithium chloride ≥ 98% was purchased from Riedel-de Haën and used as is. All NMR spectra were recorded using a Varian 300 MHz VNMRS, Varian 400 MHz Inova or Varian 600 MHz Unity spectrometer. SEC analysis, in DMAc, was performed on a setup consisting of a Waters 717 plus autosampler connected to a Shimadzu LC-10AT pump with the following column configuration: 1×PSS GRAM analytical precolumn (10 μ particle size, 8.0×50 mm), 1×PSS GRAM analytical column (10 μ particle size, 100 Å pore size, 8.0×300 mm), 2×PSS GRAM analytical column (10 μ particle size, 3000 Å pore size, 8.0×300 mm.) A Waters 2487 dual wavelength absorbance detector and a Waters 410 differential refractometer were connected in series. The SEC system was calibrated using narrow dispersity poly(methyl methacrylate) standards. SEC in THF was performed as follows: A SEC instrument equipped with a Waters 717plus Autosampler, Waters 600E system controller and Waters 610 fluid unit were used to perform SEC analyses. A Waters 2414 differential refractometer was used for detection. Two PLgel 5 μm Mixed-C columns and a PLgel 5 μm guard column were used. The oven temperature was maintained at 30 °C and 100 μL of 2 mg mL⁻¹ sample was injected into the column set. Tetrahydrofuran (THF) (HPLC grade, BHT stabilised) was used as the eluent for the analyses at a flow rate of 1 mL min⁻¹. Narrow polystyrene standards with molar masses ranging from 800–2 × 10⁶ g mol⁻¹ were used to calibrate the instrument. Molar masses obtained from SEC are reported as h-polystyrene equivalents.

Synthesis of RAFT agents

Xanthate (**1**) was synthesized as previously described by Postma et al.¹ ¹H-NMR (300 MHz, CDCl₃): δ = 1.46 (tr, 7.1 Hz, 3H), 4.68 (q, 7.1 Hz, 2H), 5.33 (s, 2H), 7.75 (m, 2H), 7.85 (m, 2H).

Dithiocarbamate (**2**) was synthesized according to a procedure described by Corpart et al.,² as follows:

Sodium hydride (1.24 g, 26 mmol) was suspended in THF (10 mL), under an argon atmosphere. A THF solution (5 mL) of *N*-methylaniline (2.14 g, 20 mmol) was added and the mixture was refluxed for ~ 10 minutes. The colour of the reaction turned green/yellow. The reaction was then cooled to room temperature, on its own accord and allowed to stir for an hour. Afterwards, it was cooled to 0 °C and carbon disulfide (2.84 mL, 47 mmol) was added, and the reaction stirred for 30 minutes. Afterwards, the reaction mixture was cooled to -15 °C and methyl 2-bromopropionate (3.33 g, 20 mmol), in a THF solution (5 mL) was added, dropwise. Afterwards the reaction was allowed to warm up to room temperature, on its own accord, and further stirred for two hours. The reaction was killed by slowly adding water (10 mL) and extracting the product into diethyl ether. The combined ether extracts were dried over anhydrous magnesium sulphate, and the product purified with column chromatography (pentane/ethyl acetate =19:1, and 0.5 % triethylamine). The second fraction (R.F. = 0.3) was determined by NMR to be the requisite product, 2: ¹H NMR (300 MHz, CDCl₃) δ: 7.49–7.39 (m, 3H), 7.28–7.23 (m, 2H), 4.66 (q, *J* = 7.03, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 1.48 (d, 3H). ¹³C NMR (300 MHz, CDCl₃) δ: 197.24, 172.88, 129.97, 129.29, 127.03, 52.76, 49.68, 17.22.

Dithiobenzoate (**3**) was synthesized according to the procedure described by Farmer and Patten.³ ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.30 ppm (s, 2H), 7.48-7.58 ppm (m, 2H), 7.64-7.69 ppm (m, 2H), 7.97-8.00 ppm (m, 1H).

RAFT-mediated polymerization of NVP monitored by *in situ* ¹H NMR

NVP (0.30 g, 2.70 mmol), RAFT agent **1** (0.15 g, 0.54 mmol) and AIBN (9 mg, 0.055 mmol) were added to 0.5 mL benzene-*d*₆. *R* = [NVP]/[RAFT] = 5 for this reaction. The volume of the solution was measured (0.89 mL) and 0.7 mL of the solution was placed in a Wilmad quick pressure valve NMR tube. Three freeze-pump-thaw cycles were performed on the sample. The tube was back-filled with argon and placed in a Varian 400 MHz Inova NMR spectrometer. A spectrum of the initial conditions was taken at 25 °C before switching the variable temperature flow gas to nitrogen, removing the sample from the spectrometer and raising the temperature to 65 °C. The polymerization was performed at 65 °C as this is the temperature at which the calculated half-life of AIBN is 10 hours. Once the temperature had stabilized, the sample was inserted. The time required for shimming the magnetic field and adjusting the deuterium feedback loop was recorded. The spectrometer was programmed to take an array of spectra, recording a scan every 5 minutes for 10 hours. Each scan was taken using 4 transients, with an acquisition time of 4 seconds and relaxation delay of 1 second. The pre-acquisition delay between scans was set to 280 seconds.

RAFT-Mediated Polymerization of NVP with RAFT agent **1** in a batch mode

A typical procedure for the batch mode RAFT mediated polymerization of *N*-vinylpyrrolidone is described. Variations in target degree of polymerization (DP), solution or bulk polymerization, and RAFT agent used are presented in Table 1 (main text):

NVP (2.0 g, 18 mmol), RAFT agent **1** (26 mg, 0.092 mmol) and AIBN (3 mg, 0.018 mmol) were placed in a Schlenk tube and three freeze-pump-thaw cycles were performed. The Schlenk tube was back-filled with argon and placed in an oil bath heated to 65 °C. Samples for NMR and SEC were taken at reaction times of 2 hours, 4 hours and 5.75 hours. Conversions were determined by ¹H NMR spectroscopy. Residual monomer was quantified from the signal at 7.07 ppm (N-CH=CHH), whilst the overlapping resonances at 2.9-4.2 ppm were used to determine the amount of residual monomer plus polymer. Residual RAFT agent was quantified from the signals at 5.33 ppm (residual R-group methylene protons) and at 7.6-7.9 ppm (residual plus converted R-group aromatic protons).

Table S1. Experimental Results for RAFT-Mediated Polymerization of NVP with RAFT agent **1** in Batch Mode

$\frac{[M]}{[I]}$	Time / min	NVP Conversion / %	RAFT agent 1 Conversion / %	$M_{n,theory}$ / g mol ⁻¹	$M_{n,NMR}$ / g mol ⁻¹	$M_{n,SEC}$ / g mol ⁻¹	\bar{D}
117	50	23	55	3300	5600	4000	1.50
117	110	42	84	5700	6800	5300	1.40
117	185	61	95	8200	8700	6400	1.39
117	245	71	97	9900	9500	7400	1.41
196	120	25	72	5900	7800	6600	1.66
196	240	46	93	10300	10300	8900	1.48
196	345	53	99	11800	10900	9700	1.47

RAFT-mediated Polymerization of NVP with RAFT agent **1 in semi-batch mode in bulk**

A typical procedure for the semi batch mode RAFT mediated polymerization of N-vinylpyrrolidone is described. Variations in target DP are presented in Table 1 (main text):

Distilled NVP (10 mL) was placed in a Schlenk tube and three freeze-pump-thaw cycles were performed. The vessel (feed tank) was then back-filled with argon. Thereafter, degassed NVP (1 mL, 9.36 mmol) was transferred to another Schlenk tube (reactor) along with RAFT agent **1** (0.013 g, 0.45 mmol) and AIBN (0.009 g, 0.055 mmol). A magnetic stirrer bar was added and three freeze-pump-thaw cycles were performed. A drop (ca. 10 mg) was taken for NMR analysis of the initial conditions. The mixture was polymerized at 65 °C for 475 minutes. After specific time intervals, samples of the polymer solution were taken for analysis. Conversions were determined by ¹H NMR spectroscopy as described earlier. Specific amounts of degassed monomer were carefully transferred to the reaction mixture using an evacuated syringe. The times when specific amounts of monomer and initiator were added are given in Table S2.

RAFT mediated semi-batch polymerization of NVP with RAFT agent **1 in 1,4-dioxane**

A typical procedure for the semi batch mode RAFT mediated polymerization of N-vinylpyrrolidone, in solution, is described. Variations in target DP, and RAFT agent used are presented in Table 1 (main text):

Feed tanks for NVP as well as 1,4-dioxane were prepared as described above. Degassed NVP (1 mL, 9.36 mmol), **1** (0.13 g, 0.45 mmol), AIBN (0.009 g, 0.55 mmol) and degassed 1,4-dioxane (0.5 ml) were added to a Schlenk tube. A magnetic stirrer bar was added and three freeze-pump-thaw cycles were performed. The Schlenk tube was then back-filled with argon. A drop (ca. 10 mg) was taken for NMR analysis of the initial conditions. The mixture was polymerized at 65 °C for 12 hours and 15 minutes. After specific time intervals, samples of the polymer solution were taken for analysis. Conversions were determined by ¹H NMR spectroscopy as described earlier. Specific amounts of degassed monomer solution in 1,4-dioxane as well as AIBN were carefully transferred to the reaction mixture using an evacuated syringe. The times when specific amounts of solvent, monomer and initiator were added are given in Table S3.

The preliminary experimental procedures described above made use of additional AIBN. However, the additional AIBN proved not to impact the observed results when eliminated, as such, all subsequent experiments were carried out without additional AIBN.

Table S2. Reagent Feed Profiles for RAFT-Mediated Semi-Batch Polymerization of Neat NVP with RAFT agent 1

Time / min	NVP added / mL	AIBN /mg
125	1.0	-
245	1.0	-
355	1.0	2.8
435	1.0	-
515	1.0	-

Table S3. Experimental results for semi-batch polymerizations of neat NVP presented in Table S2

Time / min	NVP Conversion / %	RAFT agent 1 Conversion / %	$M_{n,NMR}$ / g mol ⁻¹	$M_{n,SEC}$ / g mol ⁻¹	\bar{D}
125	61	80	2000	1500	1.19
245	61	95	3000	2000	1.20
355	57	100	4000	2900	1.22
435	60	100	6200	4200	1.20
515	60	100	8100	5700	1.21
605	62	100	10100	7600	1.23

Table S4. Reagent Feed Profiles for RAFT-Mediated Semi-Batch Polymerization of Neat NVP with RAFT agent 1

Time / min	NVP added / mL	AIBN /mg
125	1.0	-
245	2.0	2.5
380	4.0	-

Table S5. Experimental results for semi-batch polymerizations of neat NVP presented in Table S4

Time / min	NVP Conversion / %	RAFT agent 1 Conversion / %	$M_{n,NMR}$ / g mol ⁻¹	$M_{n,SEC}$ / g mol ⁻¹	\bar{D}
125	57	82	1900	2100	1.16
245	62	95	3200	2400	1.18
380	64	99	5700	4900	1.24
530	64	100	13400	10900	1.31

RAFT-Mediated Polymerization of NVP and styrene with RAFT agent 2, in a batch and semi-batch mode

Bulk and solution polymerizations of NVP and styrene, in batch and semi batch mode, with RAFT agent 2 were carried as described for described above with RAFT agent 1. The monomer/RAFT agent/initiator ratios are given in Table 1 (main text). The times when specific amounts of solvent, monomer and were added, for the solution semi batch polymerization, are given in the tables below. Polymerizations of NVP were conducted at 60 °C. NVP conversions were determined by ¹H NMR spectroscopy. Residual monomer was quantified from the signal at 7.07 ppm (N-CH=CHH), whilst the overlapping resonances at 2.9-4.2 ppm were used to determine the amount of residual monomer plus polymer. Residual RAFT agent was quantified from the signals at 4.66 ppm (residual R-group methine proton) and at 7.49-7.29 ppm (residual plus converted R-group aromatic (*m* and *p*) protons). Polymerizations of styrene were conducted at 90 °C.

Table S6. Reagent Feed Profiles for RAFT-mediated semi-batch polymerization of NVP in 1,4-dioxane with RAFT agent 2

Time / min	NVP added / mL	Dioxane added / mg
0	1.0	1.0
159	1.0	1.0
284	1.0	1.0
489	2.0	2.0

Table S7. Experimental results for semi-batch polymerizations of NVP presented in Table S6

Time / min	NVP Conversion / %	$M_{n,SEC}$ / g mol ⁻¹	\bar{D}
1309	88*	6420	1.3 1

*Conversion was determined on the final sample gravimetrically. Polymer sample was isolated by precipitation from diethyl ether, and dried under vacuum, at 40 °C, for 24 h

Table S8. Reagent Feed Profiles for RAFT-mediated semi-batch polymerization of NVP, in 1,4-dioxane, with RAFT agent 2

Time / min	NVP added / mL	Dioxane added / mg
0	0.5	0.5
200	1.0	1.0
350	1.0	1.0
495	2.0	2.0

Table S9. Experimental results for semi-batch polymerizations of NVP presented in Table S8

Time / min	NVP Conversion / %	RAFT agent 1 Conversion / %	$M_{n,NMR}$ / g mol ⁻¹	$M_{n,SEC}$ / g mol ⁻¹	\bar{D}
200	71	100	1120	1090	1.16
350	57	100	2170	1540	1.26
495	45	100	3490	3130	1.30
1420	82	100	8620	8370	1.28

Table S10. Reagent Feed Profiles for RAFT-mediated semi-batch polymerization of styrene in toluene with RAFT agent **2**

Time / min	Styrene added / mL	Toluene added / mg
0	0.5	0.5
180	0.5	0.5
360	1.0	1.0
510	2.0	2.0

Table S11. Experimental results for semi-batch polymerizations of styrene presented in Table S10

Time / min	Styrene Conversion / %	$M_{n,SEC}$ / g mol ⁻¹	\bar{D}
1309	63*	17950	2.06

*Conversion was determined on the final sample, by gravimetry. Polymer sample was isolated by precipitation from methanol, and dried under vacuum, at 40 °C, for 24 h

Bulk RAFT-Mediated Polymerization of styrene with RAFT agent **3 in a Batch Mode**

In a typical experiment, styrene (3.2 g, 30.72 mmol), RAFT agent **3** (65 mg, 0.31 mmol) and V-88 (15 mg, 0.06 mmol) were placed in a Schlenk flask and three freeze-pump-thaw cycles were performed. The Schlenk tube was back-filled with argon and placed in an oil bath heated to 90 °C. When the reaction mixture became heavily viscous, cooling in liquid nitrogen quenched the reaction. Adding toluene reduced the viscosity and the polymer was precipitated from methanol.

Solution RAFT-Mediated Polymerization of styrene with RAFT agent **3 in a Batch Mode**

In a typical experiment, toluene (5.0 mL), Styrene (3.2 g, 30.72 mmol), RAFT agent **3** (65 mg, 0.31 mmol) and V-88 (15 mg, 0.06 mmol) were placed in a Schlenk flask and three freeze-pump-thaw cycles were performed. The Schlenk tube was back-filled with argon and placed in an oil bath heated to 90 °C. When the reaction mixture became heavily viscous, cooling in liquid nitrogen quenched the reaction. Adding toluene reduced the viscosity and the polymer was precipitated from methanol.

Solution RAFT-Mediated Polymerization of styrene with RAFT agent **3 in Semi-Batch Mode**

Toluene (5.0 mL), styrene (0.45 g, 4.32 mmol), RAFT agent **3** (65 mg, 0.31 mmol) and V-88 (15 mg, 0.06 mmol) were placed in a Schlenk tube and three freeze-pump-thaw cycles were performed. The Schlenk tube was back-filled with argon and placed in an oil bath heated to 90 °C. The reaction was allowed to proceed for 5 hours before degassed styrene (2.75 g, 26.40 mmol) was added using a purged gas tight syringe. The reaction was allowed to proceed for a further 19 hours. When the reaction mixture became heavily viscous, cooling in liquid nitrogen quenched the reaction. The polymer was subsequently precipitated from methanol and dried under vacuum.

References

1. Shimoni, O.; Postma, A.; Yan, Y.; Scott, A. M.; Heath, J. K.; Nice, E. C.; Zelikin, A. N.; Caruso, F. *ACS Nano* **2012**, *6*, 1463.
2. Biadatti, T.; Charmot, D.; Corpart, P.; Michelet, D.; Zard, S.; Chimie, R., Ed.; Rhodia Chimie: France, 1998; Vol. WO1998058974 A1.
3. Farmer, S. C.; Patten, T. E. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 555.