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Poly(Boc-Acryloyl Hydrazide): Optimisation of RAFT Polymerisation Through Modulation of Temperature

Oliver Creese, Pavan Adoni, Guanlong Su, Francisco Fernandez-Trillo

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Poly(acryloyl hydrazide) is a versatile polymer scaffold readily functionalised through post-polymerisation modification with aldehydes to yield polymers with biological applications. Here we report the effect of temperature on the RAFT polymerisation N'-(tert-butoxycarbonyl)acryloyl hydrazide (1) and demonstrate that by carefully selecting this polymerisation temperature, a compromise between kinetics of polymerisation and degradation of the RAFT agent is achieved. This new methodology gives greater control over the polymerisation process, allowing the synthesis of Boc-protected poly(acryloyl hydrazide) with high degrees of polymerisation while still maintaining low dispersities. Our results provide new insights into the synthesis of functional polymers, and should be of interest to those working on the synthesis of polymers for biomedical applications by RAFT polymerisation.

Poly(Boc-acryloyl hydrazide): optimisation of RAFT polymerisation through modulation of temperature.

*Oliver Creese, Pavan Adoni, Guanlong Su, Paco Fernandez-Trillo**

School of Chemistry, and Institute of Microbiology and Infection, University of Birmingham, Edgbaston, B15 2TT Birmingham

E-mail: f.fernandez-trillo@bham.ac.uk

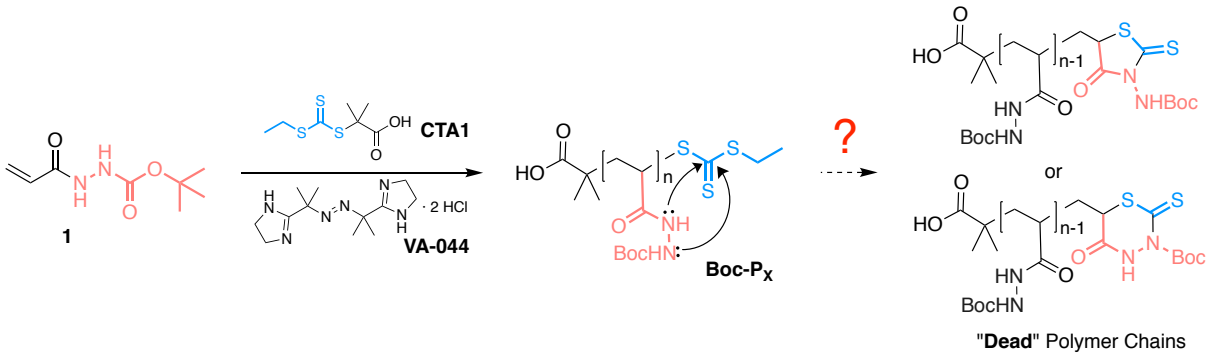
Abstract:

Poly(acryloyl hydrazide) is a versatile polymer scaffold readily functionalised through post-polymerisation modification with aldehydes to yield polymers with biological applications. Here we report the effect of temperature on the RAFT polymerisation N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**) and demonstrate that by carefully selecting this polymerisation temperature, a compromise between kinetics of polymerisation and degradation of the RAFT agent is achieved. This new methodology gives greater control over the polymerisation process, allowing the synthesis of Boc-protected poly(acryloyl hydrazide) with high degrees of polymerisation while still maintaining low dispersities.

Introduction:

Synthetic polymers are increasingly becoming an attractive means of interfacing biological systems via multivalent binding, displaying activity orders of magnitude higher than that of their monovalent components.[1-5] Multivalent effects observed by these materials are attributed to increasing the effective concentration of the active component, imparting a "chelate" affect upon the target and/or sterically increasing the stability of resulting conjugates.[1] Thus, polymers are now widely researched for biomedical applications including as antimicrobials,[6,7] as drug and gene delivery vehicles,[2,8] as biological sensors,[9,10] or as "smart" biomaterials with anti-fouling properties.[11] A common limitation when developing synthetic polymers for biomedical applications is the need to screen large libraries of compounds, which is costly and time consuming. In this regard, poly(acryloyl hydrazide) has been recently reported as a versatile platform for the synthesis and screening of polymers for biomedical applications.[12-15] Functional polymers are obtained by simple incubation of poly(acryloyl hydrazide) with functional aldehydes, both under aqueous or organic conditions,[15] and this polymer has now been applied to the development of glycan arrays,[12] pH sensitive drug-delivery[16] and nucleic acid delivery.[14,17]

In our laboratories poly(acryloyl hydrazide) was prepared following deprotection of a Boc-protected precursor **Boc-Px** (Scheme 1).[15] Reversible Addition-Fragmentation (RAFT) polymerisation of N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**) resulted in a small library of polymers. However, control over the polymerisation was lost with increasing conversion and degree of polymerisation, possibly as a result of degradation of the RAFT agent through intramolecular nucleophilic attack. This degradation has been reported in the RAFT polymerisation of other acrylamide derivatives,[18,19] including closely related methacryloyl hydrazide,[20] with better control reported when the polymerisation is carried out at low temperatures.[19,21]



Scheme 1: RAFT polymerisation of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) and potential degradation by-products.

Here, we report the effect of temperature and the nature of the initiator on the polymerisation of N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**), as a route to optimise the preparation of poly(acryloyl hydrazide). Polymerisations were done using 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (**VA-044**) as a low temperature initiator, so that the rate of generation of radicals could be readily modified as a function of temperature. Our results suggest that while increasing the temperature increases the polymerisation rate, increasing the temperature results in a faster rate at which termination is observed. A range of temperatures have been identified for which the polymerisation "outperforms" this termination and polymers with good control over molecular weight and dispersities (Đ) can be obtained. More importantly, optimised conditions allowed us to target higher degrees of polymerisation and prepare **Boc-P$_X$** with lower dispersities (Đ), not accessible with our previous conditions.[15] We believe our results highlight the importance of balancing polymerisation kinetics and RAFT agent degradation in the polymerisation of monomers containing nucleophilic moieties such as acrylamides. Moreover, this improved control over the polymerisation of Boc-protected poly(acryloyl hydrazide) will be of value when degree of polymerisation and dispersity may underpin future applications.

Experimental Section:

Materials. 2-((Ethylthio)carbonothioyl)thio-2-methylpropanoic acid (**CTA1**)[22] and N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**)[14,15] were synthesised according to protocols described in

the literature. 4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid (**CTA2**) and cyanomethyl methyl(phenyl)carbamodithioate (**CTA3**) were purchased from Sigma-Aldrich® and used without any further purification. 2,2′-Azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (**VA-044**) was purchased from Fluorochem and used without further purification. All other chemicals were purchased from Sigma-Aldrich®, Fisher Scientific®, VWR® or Acros®, and used without further purification. All solvents were Reagent grade or above, purchased from Sigma-Aldrich®, Fisher Scientific® or VWR®, and used without further purification.

Characterisation: Nuclear Magnetic Resonance (NMR) spectra were recorded on either a Bruker Avance III 300 MHz or a Bruker Avance III 400 MHz spectrometer. Chemical shifts are reported in ppm (units) referenced to the following solvent signals: dimethylsulfoxide (DMSO)-d_6 H 2.50. Gel Permeation Chromatography (GPC) was performed with a Shimadzu Prominence LC-20A fitted with a Thermo Fisher Refractomax 521 Detector and a SPD20A UV-vis Detector. poly(N'-(*tert*-butoxycarbonyl)acryloyl hydrazide) (**Boc-Px**) was analysed using 0.05 M LiBr in dimethylformamide (DMF) at 60 °C as the eluent, and a flow rate of 1 mL min^{-1}. The instrument was fitted with a Polymer Labs PolarGel guard column (50 × 7.5 mm, 5 µm) followed by two PLGel PL1110–6540 columns (300 × 7.5 mm, 5 µm). Molecular weights were calculated based on a standard calibration method using polymethylmethacrylate.

RAFT Polymerisation of N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**). In a typical kinetic experiment 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (**VA-044**) (11.7 mg, 0.036 mmol), 2-ethylthiocarbonothioylthio-2-methylpropanoic-acid (**CTA**) (40.3 mg, 0.18 mmol) and N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**) (1.666g, 8.950 mmol) were dissolved in DMSO (10.0 mL) and a 100 µL sample was taken at this stage to calculate conversion (ρ). The solution vessel was sealed with a septum and electrical tape, and degassed under argon for 25 minutes. Using a cannula, 1 mL of the solution was transferred to sealed glass vials, each degassed for 5 minutes and containing stirrer bars. Vials were then left to react at a pre-set temperature (30-150 degrees ºC) for the required amount of time. The reaction was stopped by allowing the tube to cool using a water bath and exposing it to air. 100 µL aliquots of each timepoint were taken at this stage to calculate conversion (ρ) and for GPC analysis. NMR and GPC analysis of each timepoint was carried out from the crude mixture. The natural logarithm of the inverse of the fractional concentration of monomer – $ln(M_0/M_t)$ – was plotted against time, and the data fitted using GraphPad Prism version 6.0 for Mac Os X, GraphPad Software, La Jolla California USA, www.graphpad.com. The in-built segmental line regression was used to fit the data to two intersecting lines. This model was used to identify when a change in the polymerisation kinetics was observed (t_{dead}).

Results and discussion

As reported, our initial efforts to optimise the polymerisation of Boc-protected acryloyl hydrazide **1** focused on reducing the temperature of the polymerisation.[15] RAFT polymerisation of acrylamides and methacrylamides often suffer from cleavage of the RAFT agent through intramolecular addition-elimination of the weakly nucleophilic amides to the trithiocarbonate group (Scheme 1).[19] In our previously reported conditions for the polymerisation of **1**, a change in the rate of polymerisation was observed with increasing conversion (Figure 1A), which we associated with this degradation of the terminal trithiocarbonate in the growing chain. It has been proposed that reducing the polymerisation temperature would significantly reduce the rate of this side reaction.[19] Thus, optimisation of the polymerisation was at that time done under the same conditions but using initiators with different 10 hour half-life decomposition temperatures (t_{10}) (Figure 1A). This way, rate of formation of radicals was kept as similar as possible for all polymerisations, but the temperature reduced to 50 ºC (V-65) or 44 ºC (VA-044). Despite the use of lower temperatures, in all cases, a change in the kinetics of the polymerisation was observed, although this change was not as obvious for the polymerisations performed at 44 ºC (Figure 1A). To identify when this change in rate of polymerisation was occurring, the natural logarithm of the inverse of the fractional concentration of monomer – $ln(M_0/M_t)$ – was plotted against time, and the data fitted to a segmental line regression. This model fits the data to two different lines, before and after a breakpoint. In our case, we termed that breakpoint t_{dead} because we think that after this point, termination has a predominant effect in the kinetics of the polymerisation with an increasing number of polymer chains dead. This termination was reflected on the relatively high dispersity in molecular weight (Đ =1.38-1.95) obtained for the polymers prepared with these conditions.[15] Overall, no clear benefit from reducing the temperature was observed, with a t_{dead} of approximately 4 and 4.5 hours for polymerisations at 50 ºC and 70 ºC respectively. Interestingly, t_{dead} for the polymerisation performed at 44 ºC was observed at approximately 2.5 h, which would suggest degradation was occurring faster at this temperature. This was not expected and may suggest that other mechanisms beyond the simple degradation of the RAFT agent may be at play.

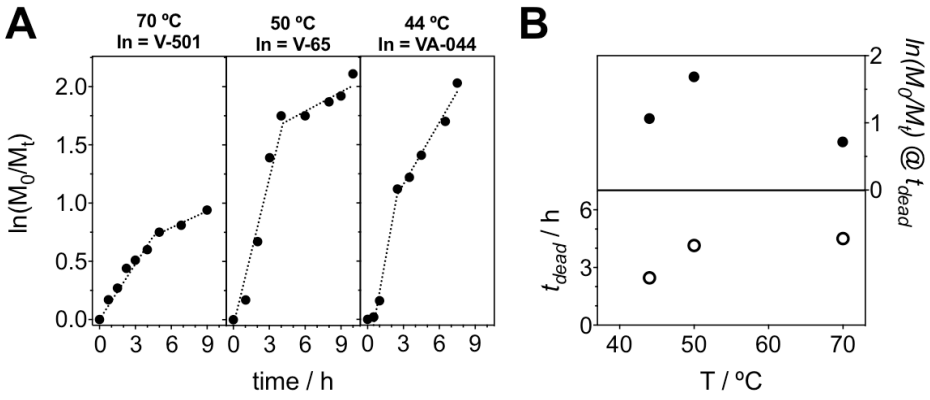


Figure 1. A) Plot of fractional concentration of monomer $ln(M_0/M_t)$ vs time for polymerisations of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) performed at different temperatures. Conditions: [M]=0.9M, [M]/[CTA]/[In]=100/1/0.2. 4,4'-Azobis(4-cyanovaleric acid) (**V-501**), 2,2'-azobis(2,4-dimethylvaleronitrile) (**V-65**), and 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (**VA-044**). Adapted with permission from Crisan, D. N.; Creese, O.; Ball, R.; Brioso, J. L.; Martyn, B.; Montenegro, J.; Fernandez-Trillo, F. Polym. Chem. **2017**, 8 (31), 4576–4584 - Published by The Royal Society of Chemistry. B) Effect of temperature on the time at which deviation from linearity for the plot of $\ln[M]_0/[M]_t$ vs time is observed (t_{dead}), and the fractional concentration of monomer $ln(M_0/M_t)$ at this point.

Attempts to perform the polymerisation at an even lower temperature (30 ºC) using VA-044 as the source of radicals resulted in a very long induction period followed by a short period of linear increase of the fractional concentration of monomer until termination was again evident (Figure S1). The maximum conversion in this case was 50% - $ln(M_0/M_t) = 0.83$, worse than that observed for the polymerisations performed at higher temperatures.

In order to determine if degradation of the RAFT agent was indeed possible at low temperatures, we attempted to synthesise a small molecule analogue which mimicked an n=1 polymer (Scheme S1). To this end, 2-bromopropionic acid (**2**) was reacted with tert-butyl carbazate, and the resulting bromine derivative **3** reacted under standard conditions for the formation of RAFT agent. ^{1}H-NMR analysis of the crude of this reaction revealed a very complex mixture, where only traces of something that could resemble trithiocarbonate **4** could be identified (Figure S3). This observation was in line with our previous results, and suggested that hydrazide containing trithiocarbonates such as **4** were very amenable to intramolecular nucleophilic attack. Attempts to isolate this trithiocarbonate **4** were unsuccessful, with the main isolated product of this reaction being tentatively assigned to a mixture of the 5- and 6-membered rings in a 6:4 ratio (Figure S4).

Seeing how lowering the temperature had no beneficial effect on the kinetics of the polymerisation of **1**, and termination was still observed, we decided to explore the use of "Ultra-Fast" polymerisation conditions in an attempt to outrun the termination reaction.[23-25] Our hypothesis was that by using a low temperature initiator such as VA-044 at a significantly higher temperature (e.g. 100 ºC) than the reported t_{10} (44 ºC), an increase in the concentration of radicals

in solution would be achieved, and thus the concentration of propagating radicals would be higher, resulting in the synthesis of polymers with better control over the Mw and Đ. This methodology is particularly suitable for fast-propagating monomers such as acrylamides, and since the rate of polymerisation is directly proportional to the concentration of these propagating radicals (and the monomer concentration, Rp = kp[M][P•]), we postulated that running the polymerisation under these conditions could outperform the termination observed under standard RAFT polymerisation conditions. In a first attempt, the polymerisation conditions previously reported by us for the polymerisation of **1** (Figure 1)[15] were modified so that the initiator used was VA-044 and the polymerisation temperature was 100 ºC. A shorter polymer was targeted this time and, as expected, the polymerisation was very fast, reaching up to 70% conversion in less than five minutes (Figure 2A, CTA:VA-044 5:1 ●). Termination could not be suppressed and a change in the rate of the polymerisation was again evident, with a t_{dead} of approximately 4.5 mins. Before t_{dead}, the polymerisation retained the features of a controlled polymerisation, with the molecular weight of the polymer directly proportional to the conversion and, more importantly, low dispersities (~1.2) (Figure 2B, left), lower than those observed with our previous conditions (~1.4).[15]

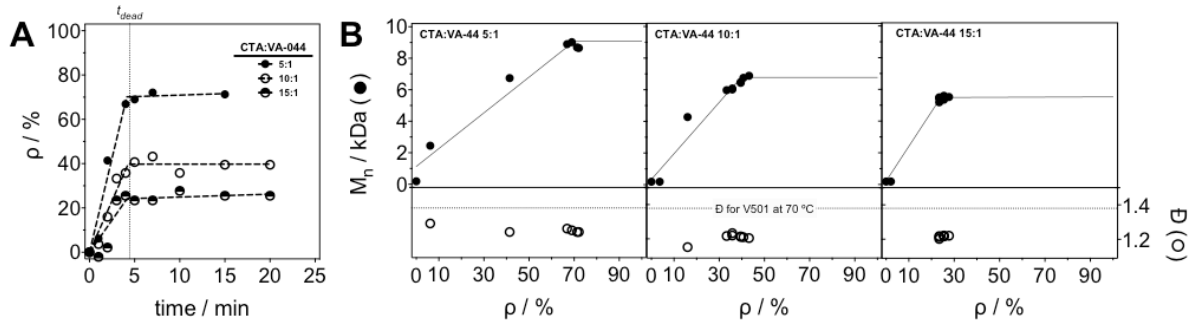


Figure 2. A) Plot of conversion $(\rho)_t$ vs time and B) measured number average molecular weight (Mn) vs. conversion (●) and dispersity in molecular mass (Đ) vs conversion (◯), for polymerisations of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) performed with different CTA:VA-044 ratios. Conditions: [M]=0.9M, [M]/[CTA]=50/1. Mn and Đ calculated by GPC using 0.05 M LiBr in dimethylformamide (DMF) at 60 °C.

These results were promising, and although termination was still observed, a significant improvement in the dispersities of the polymers was clearly obtained. We therefore explored decreasing the concentration of initiator in our polymerisations, in an attempt to increase the number of living chains, and thus optimise the dispersities obtained. However, decreasing the concentration of initiator in these polymerisations resulted in slower reactions, with no effect observed in the rate of termination (Figure 2A). As a result, the maximum conversion obtained when the CTA:VA-044 ratio was increased to 10:1 or 15:1 (40% and 24% conversion respectively) was lower than in the previous case (70%). In all cases, polymerisations at 100 ºC resulted in better dispersities than those polymerisations done under the previous RAFT conditions (Figure 2B).[15]

We decided next to run the polymerisations at 150 ºC, in an attempt to further increase the number of radicals during the reaction, and thus the rate of propagation. However, these conditions not only resulted in lower conversions (Figure S5) but a colour change of the reaction mixture from yellow to dark brown, suggesting that thermal decomposition of the trithiocarbonate group was ocurring.[26] Thermal decomposition of the RAFT agent was confirmed via ^{1}H-NMR where signals consistent with the β-elimination of the trithiocarbonate could be observed (Figure S6).[26,27]

Having identified improved conditions to run the polymerisation of **1** at 100 ºC, which resulted in similar conversions to those previously reported but improved dispersities, we decided to explore the use of these conditions to prepare polymers of higher Mw (Figure 3). Three different DPs were targeted (i.e. [**1**]/[CTA] = 50, 100 and 150), by maintaining the concentration of **1** and reducing the amount of RAFT agent and initiator used. As expected, this resulted in slower polymerisations while the time of termination (t_{dead}) was still maintained at around 4.5 mins (Figure 3A). As a consequence, polymerisations targeting 100 and 150 monomer units stopped before reaching high conversions (~ 40% and 30% respectively). Unfortunately, increasing the concentration of **1** so that the concentration of VA-044 was the same for all targeted DPs, was not possible, due to the low solubility of this monomer in DMSO. In any case, control over the molecular weight of the polymer was still observed during the first stages of the polymerisation, with the average molecular mass (M_n) increasing linearly with time until termination was evident (t_{dead}) (Figure 3B). A clear shift towards lower retention time was observed in the gel permeation chromatograms when higher DPs were targeted, suggesting that, at least during the initial phase of the reaction, the polymerisation was maintaining features of a controlled radical polymerisation.

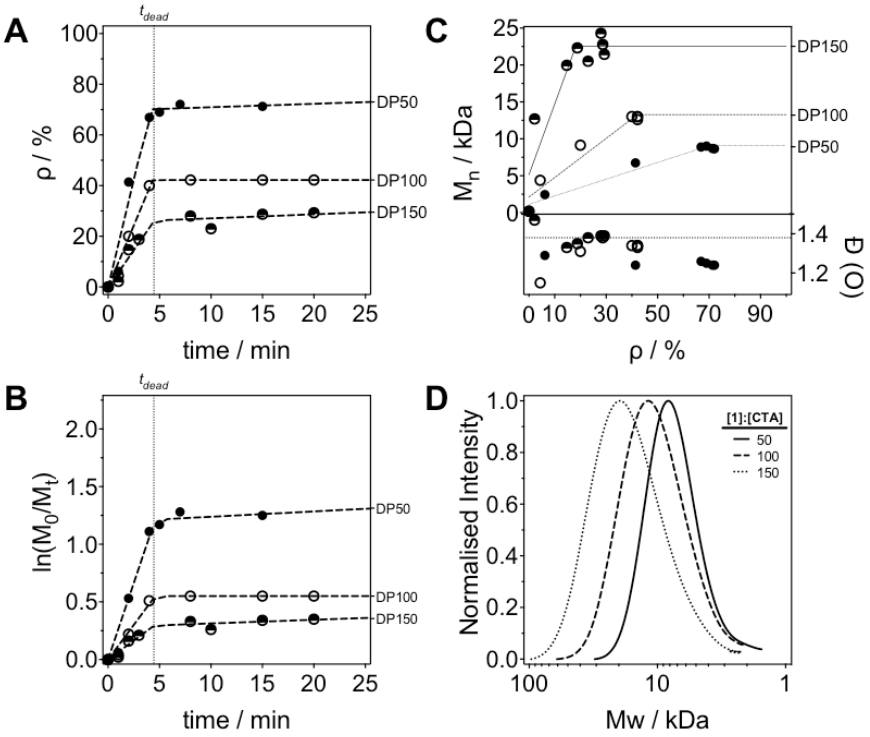


Figure 3. A) Plot of conversion (ρ) vs time, B) fractional concentration of monomer $ln(M_0/M_t)$ vs time, and C) measured number average molecular weight (Mn) vs. time (top) and dispersity in molecular mass (Đ) vs time (bottom), for polymerisations of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) performed at 100 ºC with different **1**:CTA ratios. D) GPC chromatograms of the resulting polymers at the highest conversion obtained. Conditions: [M]=0.9M, [CTA]/[VA-044]=5/1. Mn and Đ calculated by GPC using 0.05 M LiBr in dimethylformamide (DMF) at 60 °C.

At this point, our results suggested that a compromise could be obtained between increasing the rate of propagation by increasing the polymerisation temperature, and increasing the time taken for termination of the polymerisation process t_{dead} by reducing the polymerisation temperature. Therefore, we investigated polymerisations at intermediate temperatures (Figure 4). While termination was still evident for the new temperatures investigated (Figure 4A), higher conversions could be achieved for the polymerisation performed at 65 ºC (Figure 4B, ●). Temperature had a significant effect on the time when termination was evident (t_{dead}), with this inflection point happening sooner as the temperature was increased (Figure 4B, ○).

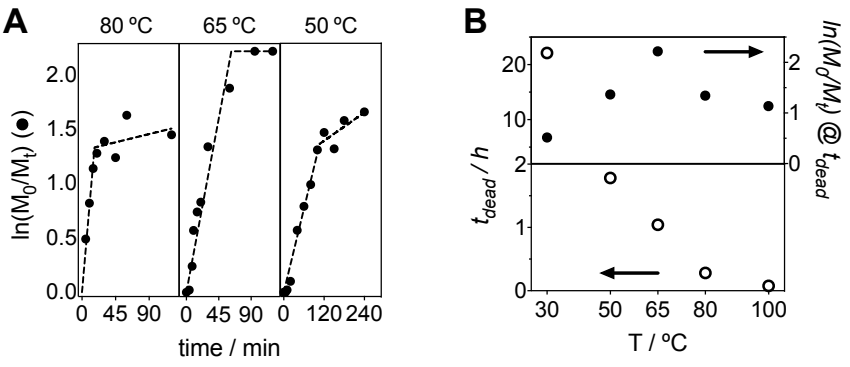


Figure 4 A) Plot of fractional concentration of monomer $ln(M_0/M_t)$ vs time for polymerisations of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) performed at different temperatures. B) Effect of temperature on the time at which deviation from linearity for the plot of $\ln[M]_0/[M]_t$ vs time is observed (t_{dead}) (◯), and the fractional concentration of monomer $ln(M_0/M_t)$ at this point (●). Conditions: [M]=0.9M, [M]/[CTA]/[VA-044]=50/1/0.2.

Seeing how running the polymerisations at 65 ºC gave the highest conversions at t_{dead} of all the conditions evaluated, we decided to target different degrees of polymerisation using these conditions (Figure 5). As before, targeting longer polymers resulted in slower rates of polymerisation, in particular for the longer polymers targeted (DP200 and DP300). While slower rates have a significant effect on the maximum conversion achieved (approx. 90%, 89%, 68% and 55% for DP 50, 100, 200 and 300 respectively), little effect was observed on the t_{dead}, with most polymerisations "stopping" after 1 h (Figure 5A). Interestingly, the polymerisation targeting 300 monomer units had a slightly longer t_{dead}, (80 min).

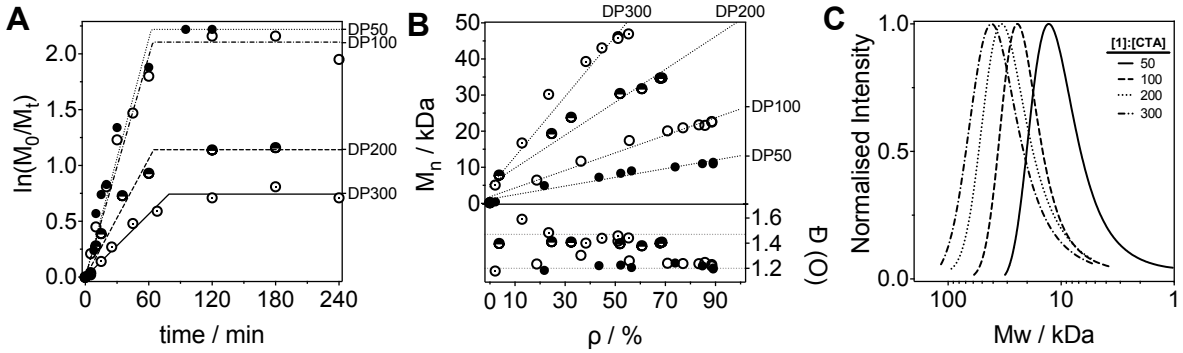


Figure 5 A) Plot of fractional concentration of monomer $ln(M_0/M_t)$ vs time. B) Measured number average molecular weight (Mn) vs. time (top) and dispersity in molecular mass (Đ) vs time (bottom), for polymerisations of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) performed at 65 ºC with different **1**:CTA ratios. C) GPC chromatograms of the resulting polymers at the highest conversion obtained. Conditions: [M]=0.9M, [CTA]/[VA-044]=5/1. Mn and Đ calculated by GPC using 0.05 M LiBr in dimethylformamide (DMF) at 60 °C.

Under these optimised conditions, the polymerisations retained features of a controlled polymerisation, with the molecular mass of the polymers increasing linearly with the conversion, and narrow dispersities in molar mass (Figure 5C). In all cases, the dispersities obtained were

similar or lower to those reported previously.[15] This was particularly the case when targeting 50 and 100 monomer units, with dispersities of approximately 1.2 throughout the polymerisations.

At this point, we decided to evaluate if further improvement could be achieved by optimizing the RAFT agent used. For an effective RAFT process where the majority of the polymer chains grow at the same rate, the reactivity of the propagating chain and the stability of the polymer-RAFT intermediate should be optimised such that the addition to the C=S and subsequent fragmentation has a higher rate than propagation.[28] Fast propagating monomers such as acrylamides often benefit from RAFT agents which favour this radical addition to the C=S, such as trithiocarbonates like **CTA1**.[28,29] However, we hypothesised that the bulky and electron-withdrawing nature of the Boc group in N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (**1**) could have an impact on the reactivity of this monomer, and thus the Z-group in the RAFT agent could be modified.

Two new RAFT agents were thus tested for their efficacy as charge transfer agents towards our monomer, each with Z substituents that stabilised or destabilised the polymer-RAFT intermediate, when compared to **CTA1**. Polymerisations were performed at 65 ºC and a DP of 200 was targeted. When **CTA2** (Z = Ph) was used, a slower polymerisation was observed (Figure S7A, ◯), in agreement with the additional stabilisation of the intermediate radical provided by the phenyl group. However this decrease in rate of polymerisation also resulted in lower conversions, with no significant changes to t_{dead} observed (Figure S7A, ◯). While these conditions showed some features of a controlled polymerisation, with low dispersities in molecular mass (Figure S7C, ◯), the resulting Mw for the polymers obtained were significantly higher than those where trithiocarbonate **CTA1** was used (Figure S7B, ● for CTA1 and ◯ for CTA2). Alternatively, polymerisations performed with **CTA3** (Z= N(Me)Ph) displayed faster reaction rates (Figure S7A, ◉) that we attribute to the low stability of the intermediate radical formed for dithiocarbamates. Unfortunately, these polymerisation conditions did not show any of the features of controlled polymerisations, with a decrease of Mw at high conversions (Figure S7B, ◉) and an increase in dispersity as the polymerisation proceeded (Figure S7C, ◉). In line with these observations, the Mw obtained this way for poly(N'-(tert-butoxycarbonyl)acryloyl hydrazide) was significantly higher than that obtained using **CTA1** (Figure S7D, ●), despite both polymerisations reaching similar final conversions (Figure S7A).

Conclusion

In conclusion, RAFT polymerisation of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) has been optimised by a judicious choice of temperature, allowing access to polymers with significantly improved control and shorter polymerisation times. Our results highlight that the polymerisation of acrylamides via RAFT can be severely hampered by the degradation of the chain transfer again and that, under some circumstances, this degradation cannot be eliminated

but rather outperformed if the rate of polymerisation is tuned. We demonstrate that by using a low-temperature initiator such as VA-044, optimal polymerisations conditions can be achieved at 65 ºC. This way, poly(N'-(tert-butoxycarbonyl)acryloyl hydrazide)s with high degrees of polymerisation could be obtained while still maintaining low dispersities. Finally, we demonstrate that no benefit is obtained when trithiocarbonates are replaced with dithioesters or trithiocarbamates, as the chain transfer agents.

Author contributions.

PFT, OC and PA designed the work. OC, PA and GS perfomed all the experimental work. OC and PFT analysed the data and wrote the paper, with all other authors contributing to the final version of the manuscript.

Acknowledgments

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Supporting Information

Poly(Boc-acryloyl hydrazide): optimisation of RAFT polymerisation through modulation of temperature.

*Oliver Creese, Pavan Adoni, Guanlong Su, Paco Fernandez-Trillo**

School of Chemistry, and Institute of Microbiology and Infection, University of Birmingham, Edgbaston, B15 2TT Birmingham

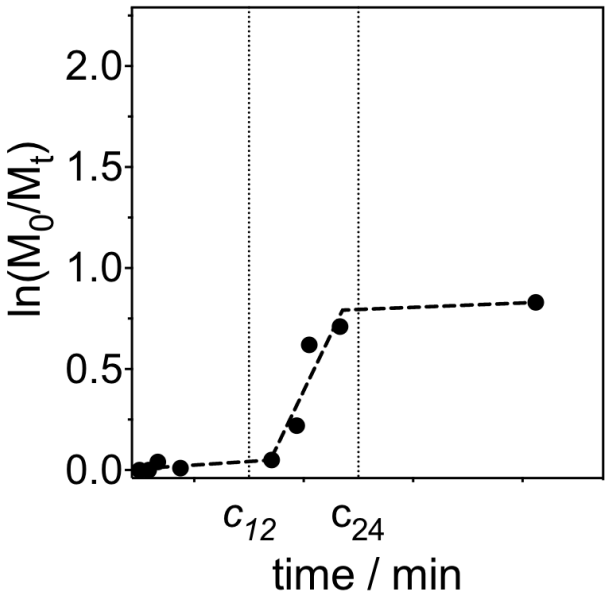
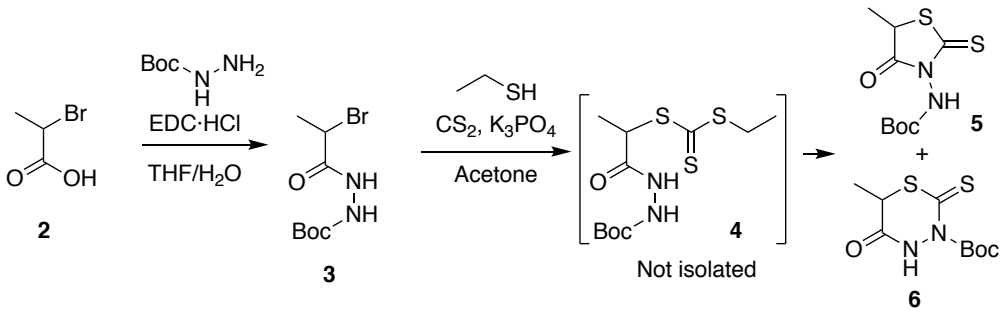


Figure S1. Plot of $ln(M_0/M_t)$ vs time for the polymerisation of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) at 30 ºC. Conditions: [M]=0.9M, [M]/[CTA]/[VA-0 44]=50/1/0.2.

Small molecule analogue of a DP= 1 of N'-(*tert*-butoxycarbonyl)acryloyl hydrazide (1).



Scheme S1: Attempted route for the synthesis of a DP= 1 analogue of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**).

***tert*-butyl 2-(2-bromopropanoyl)hydrazine-1-carboxylate (3):** 2-Bromopropionic acid (**2**) (10 g, 59.9 mmol) and tert-butyl carbazate (6.56 g, 49.6 mmol) were dissolved in a 2:1 mixture of water/THF (180 ml). N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (13.3 g, 69.5 mmol) was added in portions to the solution over 15 minutes and the mixture was left stirring for 3h at room temperature. The solution was extracted into Teac (3 x 60 ml) and a basic work-up performed with $NaCO_3$ (3 X 60 ml). The organic layer was further washed with water (2 x 60 ml), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure to leave a white solid. This solid was then recrystallised using ethyl acetate to afford white crystalline material which was washed with ice cold diethyl ether and dried under reduced pressure (8.9 g, 64 %): ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm) 9.9 (s, 1H), 9.0-8.3 (s, 1H), 4.45 (q, 1H), 1.65 (d, 3H), 1.38 (s, 9H).

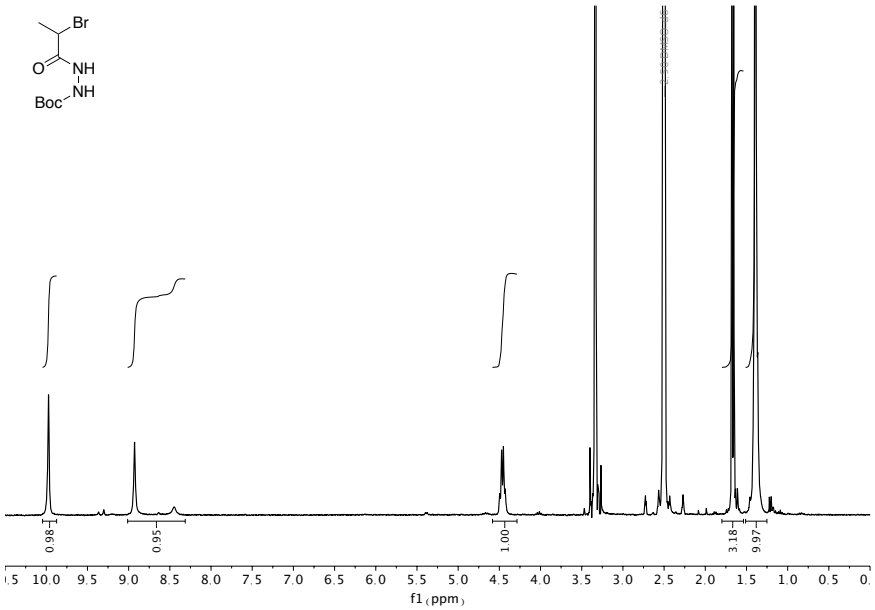


Figure S2: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of *tert*-butyl 2-(2-bromopropanoyl)hydrazine-1-carboxylate (**3**).

***tert*-butyl 2-(2-(((ethylthio)carbonothioyl)thio)propanoyl)hydrazine-1-carboxylate (4) (not isolated):** Ethanethiol (0.49 ml, 6.59 mmol) was added to a suspension of K_3PO_4 (1.4 g, 6.59 mmol) in acetone (20 ml) and was left stirring at room temperature for 10 minutes. CS_2 (1.09 ml, 6.59 mmol) was then added and the reaction mixture was left for a further 10 minutes. *tert*-butyl 2-(2-bromopropanoyl)hydrazine-1-carboxylate (**1**) (1.6 g, 5.99 mmol) was added in one portion and the mixture left to react for 13 hours. The solvent was then removed under reduced pressure and HCl (100 ml, 1 M) was added to the crude of the reaction. The resulting mixture extracted into DCM (2 x 100 ml). The organic layer was then washed with water (2 x 100 ml) and brine (2 x 100 ml), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The resulting orange oil was purified by column chromatography using a 7:3 ratio of diethyl ether and hexane, then dried under reduced pressure to leave a viscous orange liquid (0.12 g, 7 %) which consisted of two compounds, none of which is the title compound. a; 1H NMR (300MHz, $CDCl_3$) δ (ppm) 10.3-9.7 (1H, s, NH), 4.66 (q, 1H), 1.58 (d, 3H), 1.44 (s, 9H) and b; ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm) 10.3-9.7 (1H, s, NH), 4.73 (q, 1H), 1.59 (d, 3H), 1.44 (s, 9H).

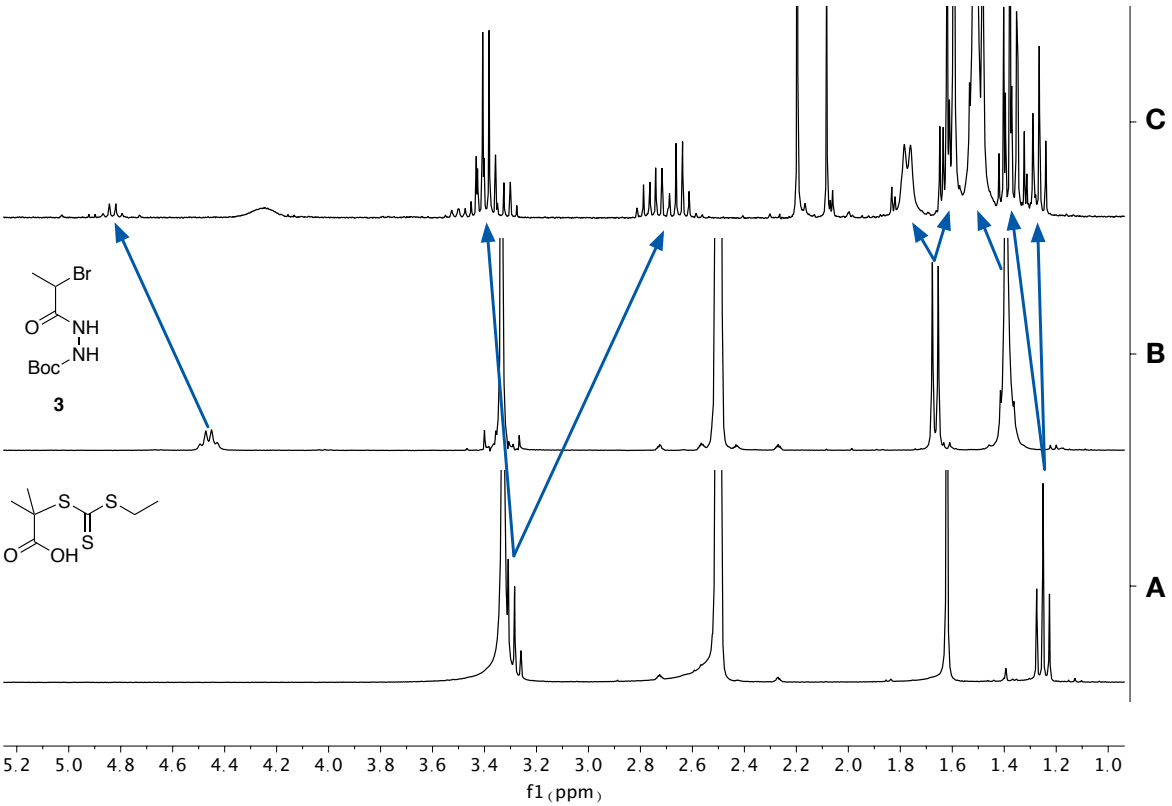


Figure S3: **A**) ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of crude of the reaction of ethanethiol with carbon disulfide and *tert*-butyl 2-(2-bromopropanoyl)hydrazine-1-carboxylate (**3**). **B**) ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of *tert*-butyl 2-(2-bromopropanoyl)hydrazine-1-carboxylate (**3**). **C**) ^{1}H NMR (300 MHz, DMSO) spectrum of 2-((ethylthio)carbonothioyl)thio-2-methylpropanoic acid (**CTA1**).

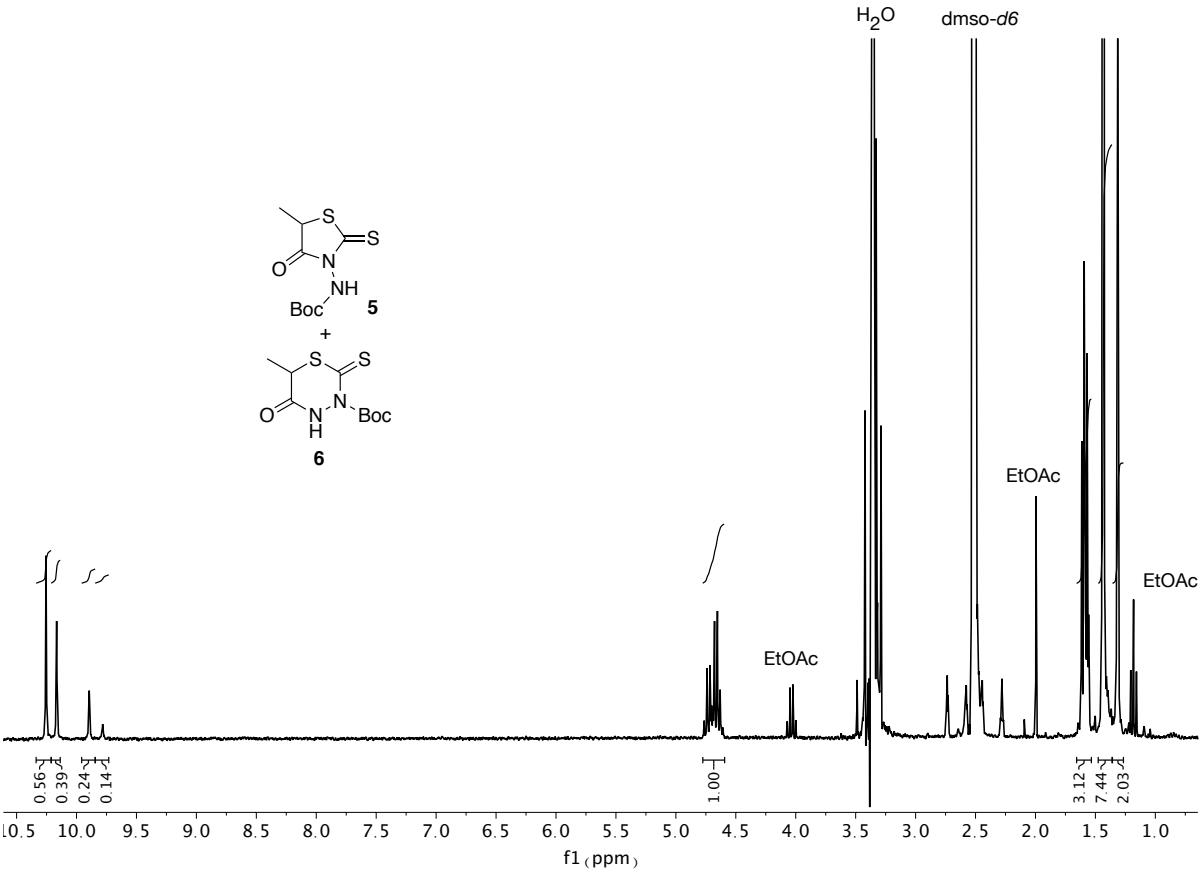


Figure S4: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of the main fraction isolated following the reaction of ethanethiol with carbon disulfide and *tert*-butyl 2-(2-bromopropanoyl)hydrazine-1-carboxylate (**3**).

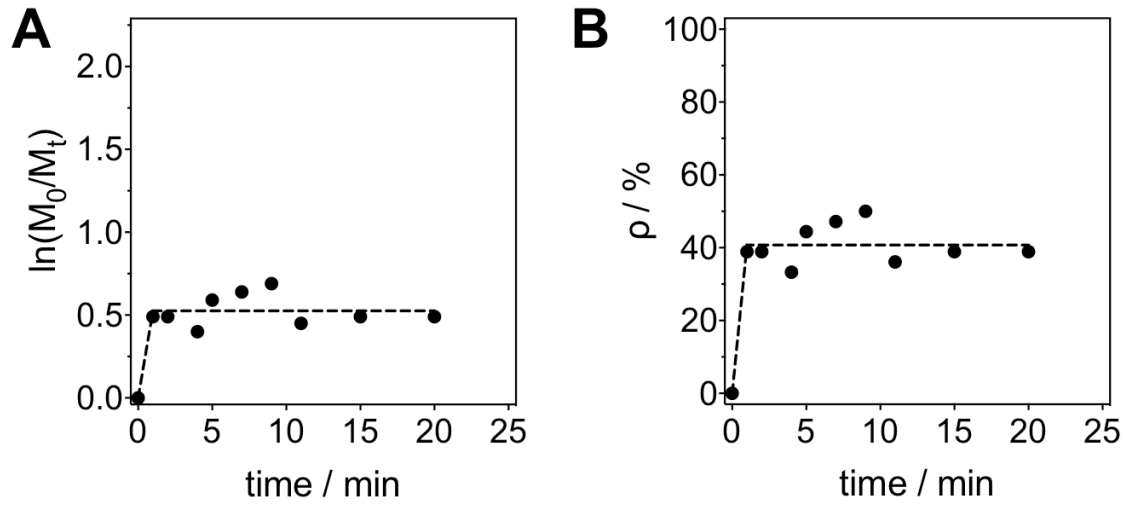


Figure S5: Plot of $ln(M_0/M_t)$ vs time (**A**) and conversion (ρ) vs time (**B**) for the polymerisation of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) at 150 ºC. Conditions: [M]=0.9M, [M]/[CTA]/[VA-044]=50/1/0.2.

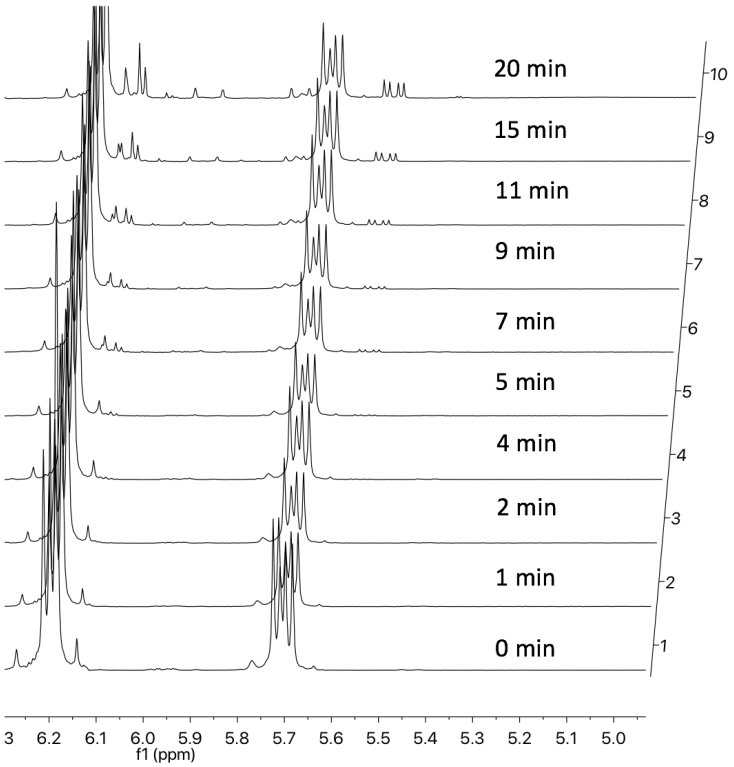


Figure S6: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum showing vinyl region at varying time points in the polymerisation of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) at 150 ºC. Conditions: [M]=0.9M, [M]/[CTA]/[VA-044]=50/1/0.2. New vinyl protons can be observed from 7 minutes, suggestive of β-elimination products.

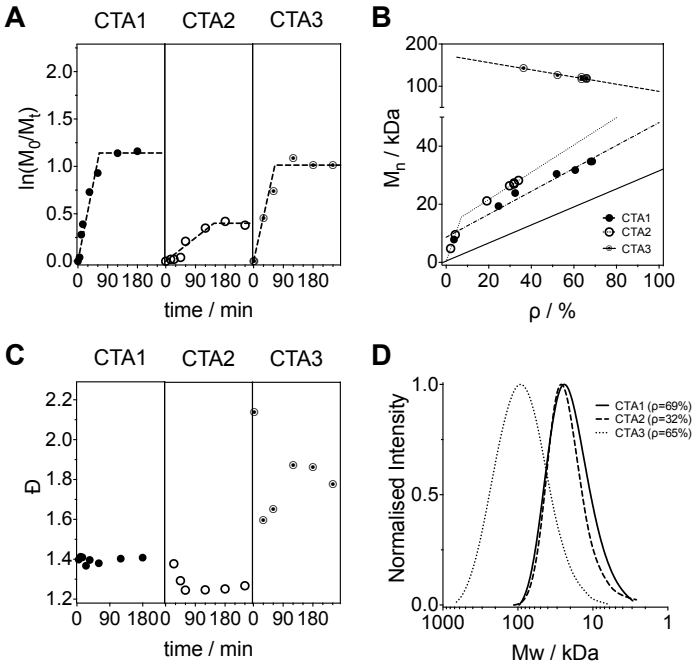


Figure S7: **A**) Plot of fractional concentration of monomer *ln(M_0/M_t)* vs time; **B**) measured number average molecular weight (Mn) vs. time; **C**) dispersity in molecular mass (Đ) vs time; and **D**) GPC chromatograms of the resulting polymers at the highest conversion obtained, for polymerisations of N'-(tert-butoxycarbonyl)acryloyl hydrazide (**1**) performed at with different chain transfer agents. Conditions: [M]=0.9M, [**1**]/[CTA]=200/1, [CTA]/[VA-044]=5/1, 65 ºC. Mn and Đ calculated by GPC using 0.05 M LiBr in dimethylformamide (DMF) at 60 °C.