Pyrazole carbodithiolate-driven iterative RAFT single-additions†

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In this Communication, we comprehensively investigated substituent effects relevant to iterative reversible activation fragmentation chain transfer (RAFT) single unit monomer insertion (SUMI) reactions. Through the use of the pyrazole carbodithiolate (PCDT) “Z-group” as the chain transfer component in RAFT SUMI, we show the importance of “Z-group” effects and its interplay with “R-group” (the carbon-centred radical precursor) effects. We also expanded the scope of RAFT SUMI to new monomer types and sequences thereof. As such, the C–S bond dissociation/reformation steps were found to be crucial factors in SUMI, and it was found that general substituent effects must be wholistically examined for every step of this reaction. This stands in contrast with conventional knowledge of RAFT polymerisation, where the main consideration is often centred around the propagation stage, i.e., the key C–C bond formation step. Indeed, contrary to SUMI, the latter characteristic was observed in the analogous alternating copolymerisation.

The bottom-up study of macromolecular sequence remains one of the major open questions in polymer science.1 This question primarily concerns the translation of small-molecule synthesis to polymer synthesis, and the extent to which the chemistry of macromolecules is driven by their microstructure.2 This culminates in sequence-defined polymers and biomacromolecules. Many groups have sought to realise sequence specificity in increasingly diverse polymer backbones.2 In the first instance, polymers such as those analogous to native biomacromolecules (e.g., phosphodiesters, carbamates) have been synthesised in a sequence-defined fashion, to those diverging significantly from biomacromolecules via click/ligation chemistry (e.g., thiol–ene, Diels–Alder cycladditions, [3+2] azide–alkyne cycloadditions).3–7 In latter case, reaction feasibility is a guiding principle for choice of backbone, as opposed to structure.

Most interestingly, the monomer single-addition analogue of RAFT polymerisation, single unit monomer insertion (SUMI), sits at a direct interface between small-molecular chemistry and polymer chemistry.8 RAFT SUMI processes can be hypotethically iterated to furnish polymers of an increasingly precise sequence in a multi-chain growth process without protecting groups. The key hurdle towards realising this is finding monomers which balance consistent reactivity for single-addition while being selective against oligomerisation and termination.

Initial studies of RAFT SUMI by the Zard, Moad and Junkers groups were groundbreaking in their novelty and scope but were not as concerned with indefinite iteration of the chemistry.9–14 Our group has studied combinations of electron-rich/deficient monomers normally used in alternating copolymerisations to ensure activity, while minimising homopolimerisation.15,16 Similarly, the Xiao group has developed the iterative SUMI of cyclic ketene acetals.17,18 The You group have even used the RAFT SUMI chemistry of polyfunctional-maleimides for step-growth polymerisations.19,20 From these developments, it remains a challenge to iterate these SUMI processes indefinitely while maintaining the aforementioned selectivity. Our previous work partially addressed the practical aspect of this challenge through implementing solid-phase synthesis.21 However, as concluded there, it remains to find an ideal SUMI monomer system with suitable reactivity and minimal side-reactions, a subject of investigation by many groups including our own.15,16,22–25

In order to expand the scope of monomers (and sequences thereof) applicable to iterative RAFT SUMI, we were interested in using pyrazole carbodithiolate derives as chain-transfer agents, spurred on by reports of their capacity as “universal” chain transfer agents for RAFT polymerisation.26,27 We, therefore, hypothesised that restrictions around SUMI would be overcome through altering the chain transfer agent (CTA, Fig. 1). To that end, we experimentally and computationally investigated iterative additions of nitrile and phenyl-containing monomers in great detail, given their promise in single-additions but relative inability to be iterated further. We also looked to investigate how

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these outcomes extended to the analogous RAFT alternating copolymerisation.

Our investigations started with the trithiocarbonate-driven fumaronitrile SUMI of FCN-Ind sequences. In either solid-phase (Rink@CVA-Ind-FCN-Ind-(C_{12})TTC) or solution phase (PhMeCH-FCN-Ind-(C_{4})TTC, see ESI† Appendix for procedures and data), FCN-Ind sequences were inert to such reactions, the latter being consistent with previous work from our group (Fig. 2A).\textsuperscript{16} This was initially attributed to penultimate unit effects (influence of the monomer unit adjacent to the radical-forming terminal monomer unit on reactivity) as reported in the analogous alternating copolymerisation (Fig. 2A).\textsuperscript{28} It was also unlikely due to slow initiation, as other monomers (e.g., maleimides and fumarates) could be trapped from this same 2-mer in our previous work.\textsuperscript{16} We also found that adding a co-coordinating metal (namely, Gd(\textit{iii}) due to its nitrile coordination\textsuperscript{29,30}) or changing the terminal unit (radical-forming monomer unit) to a more conformationally flexible trans-anethole unit with a similar C–S bond-dissociation enthalpy\textsuperscript{23} (PhMeCH-FCN-TransAn-(C_{4})TTC) yielded no difference in reaction outcome. We also considered changing the reaction solvent, but reactant insolubility became a hindrance.

This, then compelled us to investigate various scenarios of nitrile terminal and penultimate unit effects in trithiocarbonate-driven SUMI. One involved adding fumaronitrile to IBN-(C_{12})TTC (Fig. 1) and the other to IBN-Ind-(C_{12})TTC (see ESI† for Nomenclature). In the latter case, the nitrile on the IBN “penultimate” unit (not strictly a penultimate unit as it is not from a monomer, but will be referred as such in this case for the sake of comparison) was on a freely rotatable C–C–CN bond, translating in a more facile reaction to the SUMI product and, remarkably, with identical kinetics to addition onto PhMeCH-(C_{4})TTC (Fig. 2B, Fig. S1-2, ESI†), and, therefore, no apparent penultimate unit effect. In the former case, the terminal unit presented an unfavourable polarity mismatch, but interestingly still yielded the SUMI product, despite the α,β,γ-trinitrile substitution on the SUMI adduct. This was, albeit not reproducibly, and in low yield (∼9% yield).

We then moved to investigate these reactions under pyrazole carbodiithiolate chain transfer. In the first instance, fumaronitrile SUMI with a styrenic “R-group” (PhMeCH-PCDT) was almost eight times more rapid ($k_{\text{app}} = 0.62$ h$^{-1}$ vs. $0.084$ h$^{-1}$) than the analogous trithiocarbonate (PhMeCH-(C_{4})TTC) (Fig. 3A and Fig. S1-3, ESI†). Furthermore, and even more remarkably, fumaronitrile SUMI onto the corresponding polarity-mismatched isopentyl nitrile “R-group” (IPN-PCDT, Fig. 1) consistently yielded more...
product than from the trithiocarbonate (maximum yield 40%, prior to decomposition, i.e., $t > 13 \text{ h}$, $\sim$60% conversion) and was even faster than PhMeCH-(C$_1$)TTC (Fig. 3B and Fig. S1-4, ESI†).

We also found that the 4-chloro derivative of our pyrazole carbodiethiolate chain transfer agent [IPN-(Cl)PCDT] was equally effective in these SUMI processes. This facility of SUMI onto (chloro)pyrazole carbodiethiolate CTAs also extended to styrene derivatives such as indene and styrene itself (Fig. S1-5 and S1-6, ESI†), with no penultimate unit effects of its own observed (Fig. S1-7, ESI†).

When synthesising 3-mers, fumaronitrile penultimate unit effects most remarkably seemed to be reversed (i.e., promoting, rather than hindering SUMI) under pyrazole carbodiethiolate chain transfer. Specifically, fumaronitrile SUMI onto R-FCN-Ind-PCDT 2-mers (R = IPN, PhMeCH) were surprisingly facile, with almost full conversion observed in 2 h in both cases (Fig. 3C, Fig. S1-8 and S1-9, ESI†) and in high yield (both $\sim$85% yield). These were the fastest fumaronitrile SUMI reactions in this study ($k_{app} > 1.5 \text{ h}^{-1}$ vs. $k_{app} = 0.62 \text{ h}^{-1}$ for PhMeCH-PCDT), in distinct contrast to the complete inactivity of the analogous trithiocarbonate species.

A brief survey of other monomers also found that fumarates (DiEtFum) and vinyl ethers (IBVE) exhibited a facile SUMI under pyrazole carbodiethiolate chain transfer. An interesting monomer was cinnamonitrile (CCN), which underwent no reaction with IBN-(C$_{12}$)TTC. However, under PCDT chain transfer (IPN-PCDT), two regiosomers of the SUMI adduct ($\alpha$-cyano-$\beta$-phenyl - $\alpha$-Ph-$\beta$-CN, or $\alpha$-phenyl $\beta$-cyano - $\alpha$-CN-$\beta$-Ph) were isolated in 74% total yield (5 h irradiation) and $\alpha$-Ph-$\beta$-CN: $\alpha$-CN-$\beta$-Ph = 3:1 roughly corresponding to the differences in reactivity towards either half. SUMI also didn’t proceed with a styrenic “R-group” (PhMeCH-PCDT) under similar conditions, due either to strain or a polarity mismatch in each regioisomeric transition state.

To further understand our experimental results, we ran quantum calculations of key reaction intermediates (see ESI† Fig. S2 for more details) with ORCA5.0.4.31 According to previous work in our group, the initial bond C–S dissociation ($\Delta G_{\text{Frag}}$, Fig. 4A, red – analogous to homolytic cleavage), radical–alkene addition ($\Delta G_{\text{Add}}$, Fig. 4A, purple) and final C–S reformation ($\Delta G_{\text{Reform}}$, Fig. 4A, cyan – analogous to radical–radical recombination) influence the thermodynamics of SUMI.32 It must be noted that these steps are purely thermodynamic and don’t necessarily correspond to exact mechanistic steps as in a kinetic calculation. With this in mind, we calculated $\Delta G$ of these steps for fumaronitrile SUMI onto chain transfer agents with two different “Z-groups” and “R-groups”, namely, simplified models of IBN-(C$_1$)TTC, IBN-PCDT, PhMeCH-(C$_1$)TTC, PhMeCH-PCDT (Fig. S2-1, ESI†).

Calculations revealed that these SUMI processes have weak but favourable overall thermodynamic driving forces (Fig. 4B), originating from favourable radical addition and C–S bond fragmentation/reformation terms. Overall, $\Delta G_{\text{SUMI}}$ varied only slightly, decreasing in the order IBN-(C$_1$)TTC ($\sim$30 kJ mol$^{-1}$), IBN-PCDT ($\sim$32 kJ mol$^{-1}$), PhMeCH-(C$_1$)TTC ($\sim$32 kJ mol$^{-1}$), PhMeCH-PCDT ($\sim$33 kJ mol$^{-1}$) (Fig. 4B). However, the main variation in $\Delta G_{\text{SUMI}}$ originated from the C–S components, themselves varying by 2.5–3 orders of magnitude. For instance, $\Delta G_{\text{Reform}}$ for IBN-PCDT was only 163 kJ mol$^{-1}$, which was lower than $\Delta G_{\text{Frag}}$ for PhMeCH-(C$_1$)TTC and PhMeCH-PCDT.

Interestingly, considerable substituent effects were observed in these systems. In the first instance, modifying the “Z-group” from TTC to PCDT lowered $\Delta G_{\text{SUMI}}$. More surprisingly, remote substituent effects on $\Delta G_{\text{Reform}}$ were also observed. Regardless of “Z-group”, we found that adducts with R = IBN had a $\Delta G_{\text{Reform}}$ lower than the corresponding R = PhMeCH adducts by around 10 kJ mol$^{-1}$. We attribute this to enhanced delocalisation of the intermediate cyano-radical, possibly from through-space electrostatic effects. This remote substituent effect largely offset the lower $\Delta G_{\text{Frag}}$ observed for IPN-PCDT and IPN-(C$_{12}$)TTC compared with with PhMeCH-(C$_1$)TTC and PhMeCH-PCDT. Overall, these calculations highlight the importance of considering both “R-group” and “Z-group” effects in tandem, and with respect to every reaction step. They also can explain how SUMI involving unfavourable terminal/penultimate unit effects could be facile under PCDT chain transfer.

Finally, we turned our attention to the analogous alternating copolymerisations. The key differences here with SUMI are that monomer concentration is in massive excess of radical and chain-transfer agent concentration, and that chain transfer involves degenerate states. Reaction kinetics are therefore considered independent of chain transfer (with marginal rate retardation).33,34 However, this paradigm has been updated recently, with rate retardation from chain transfer being a consistent feature of RAFT.35,36 With this in mind, we observed that the kinetics of PET–RAFT alternating copolymerisation of indene and fumaronitrile was nearly identical with either a PCDT or a TTC (CTA = IPN-PCDT, IBN-(C$_1$)TTC with [FCN]: [Ind] : [CTA] = 100 : 100 : 1) (Fig. S3-1 and S3-2, ESI†). In both cases, the kinetics was found not to follow zeroth, first or second order behaviour. The GPC molecular weight evolution over time also remained similar, converging to a limiting molecular weight of sorts. Therefore, in alternating copolymerisations, substituent effects relevant to propagation (C–C bond formation) eventually dictate the overall chemistry (Fig. S3-1–S3-4, ESI†).

In conclusion, our investigations of the PET–RAFT SUMI of fumaronitrile and styrenic derivatives, in the first instance, reinforced the idea that chain transfer, not simply radical–alkene addition is crucial in SUMI. Indeed, substituent effect...
considerations made for the radical–alkene addition (C–C bond formation) step must also be made for the C–S bond dissociation/formation steps. Importantly, these can act independently of each other. Therefore, changing the chain transfer agent from trithiocarbonates to pyrazole carbodiimolates expanded the scope of PET–RAFT SUMI to new monomers and to potentially unfavourable addition sequences. All these subtleties in SUMI chemistry were completely lost when extrapolating to the analogous alternating copolymerisation, where alkene addition was paramount in the kinetics, with chain transfer being less significant.

The results from this study may signal a means to iterate PET–RAFT SUMI of this type to higher chain lengths with potentially fewer impurities. Furthermore, this work serves as a small example of the disconnect between small molecular and macromolecular chemistry. However, it remains to address the control of stereochemical sequence and to further derivitise towards truly aperiodic polymers.

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Data availability
The data supporting this article has been included as part of the ESI.

Conflicts of interest
There are no conflicts to declare.

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