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4-Halogeno-3,5-dimethyl-1*H*-pyrazole-1-carbodithioates: versatile reversible addition fragmentation chain transfer agents with broad applicability

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Abstract

Pyrazole-based dithiocarbamates are versatile reversible addition fragmentation chain transfer (RAFT) agents that provide molar mass and dispersity (*Đ*) control over the radical polymerization of both more and less activated monomers (MAMs and LAMs). In this paper we report on theoretical and experimental findings demonstrating that their activity as RAFT agents can be significantly enhanced by introducing electron-withdrawing substituents to the pyrazole ring. This enhancement is most noticeable in methyl methacrylate polymerization where product molar masses are more accurately predicted by the RAFT agent concentration, and significantly lower *Đ* values, with respect to those seen with the parent RAFT agent under similar conditions, are observed. Thus, use of 4-chloro-3,5-dimethyl-1*H*-pyrazole-1-carbodithioate provides a poly(methyl methacrylate) with the anticipated molar mass and *Đ* as low as 1.3 at high monomer conversion. Good control is retained for monosubstituted MAMs, styrene, methyl acrylate and *N*,*N*-dimethylacrylamide. Low dispersities and less molar mass control are also achieved for homo- and copolymerizations with the LAM vinyl acetate, albeit with some retardation.

Supporting information may be found in the online version of this article.

Keywords: RAFT polymerization; reversible deactivation radical polymerization; pyrazole; radical polymerization; controlled or living polymerization

INTRODUCTION

Reversible addition fragmentation chain transfer (RAFT) polymerization[1] is a reversible deactivation radical polymerization.[2,3] It is a powerful method for the preparation of a diverse range of polymer architectures with narrow molar mass distributions, and well-defined end-groups and compositions.[4] While the impact of thiocarbonylthio RAFT polymerization has been widespread,[5–10] some limitations still exist with respect to scope and utility of individual agents.[11] The dithiocarbamates are a versatile class of RAFT agents with widespread applicability with respect to monomer type.[12–16] Their activity as a class forms a continuum with the activity of a particular dithiocarbamate being determined by the specific Z group, i.e. the substituents on the dithiocarbamate nitrogen (Fig. 1). Early work showed that with appropriate choice of Z, very good control (low *Đ*, little retardation) could be obtained over the polymerization of either more-activated monomers (MAMs; (meth)acrylates, styrenes, (meth)acrylamides) or less-activated monomers (LAMs; vinyl esters, vinyl amides, allyl monomers). It is also possible to switch the activity of certain dithiocarbamates to provide good control over both MAMs and LAMs. These RAFT agents enabled the preparation of low-dispersity (low-*Đ*) poly(MAM)-*block*-poly(LAM)s by sequential monomer addition.[17–23] A few dithiocarbamates (those with ‘ZC(=S)S—’ as shown in the centre of Fig. 1) show some capacity for control over the polymerization of both MAMs and LAMs. However, activity with respect to one or both monomer classes is generally compromised.[15,16,24]

Recently, we reported on a class of dithiocarbamates based on the 3,5-dimethylpyrazole ‘Z’ group.[24] RAFT agents **3** and **4** (Fig. 2) provide the ability to control the polymerization of both MAMs and LAMs and, importantly, they allowed the preparation of a low-*Đ* poly(MAM)-*block*-poly(LAM) (specifically,

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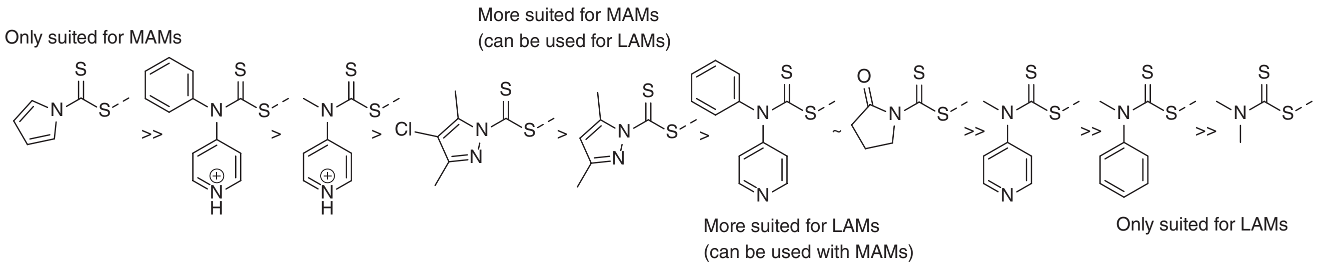


Figure 1. Effect of dithiocarbamate 'ZC(=S)S—' groups on activity of RAFT agents in radical polymerization. MAM, more activated monomer; LAM, less activated monomer. (Figure adapted from Gardiner *et al.*[24] © Royal Society of Chemistry.)

poly(*N*,*N*-dimethylacrylamide)-*block*-poly(vinyl acetate)) without a need for switching. Low-*Đ* poly(MAM)-*block*-poly(LAM)s have previously been produced by making use of the switchable cyanomethyl *N*-methyl-*N*-(pyridin-4-yl)carbamodithioate **8/8-H**$^+$ (Fig. 2).[21] The pyrazole-based RAFT agents appear equivalent to the trithiocarbonates (e.g. **1** and **2**) in their ability to control the polymerization of monosubstituted MAMs producing polymers with defined molar mass and similarly low *Đ*. However, unlike the trithiocarbonates, they can also be used to control the polymerization of the LAM vinyl acetate (VAc), and we assume other LAMs, albeit with some retardation.[24] In addition, **3** and **4** can be stored at ambient temperature and have the distinct advantage over trithiocarbonates in that the RAFT agents and the derived polymers do not develop significant odour upon use or storage due to the absence of pathways that generate thiols. However, a constraint on usage of the pyrazole-based RAFT agents is that **4** provides only limited control over polymerization of the 1,1-disubsituted monomer methyl methacrylate (MMA) with M_n being slightly greater than expected and $Đ > 1.5$ for the several conditions examined.

It is well known that the introduction of electron-withdrawing group to 'Z' or 'R' can significantly enhance the transfer constants (C_{tr}) of RAFT agents, particularly for the case of trithiocarbonates[25] and aromatic dithioesters.[26,27] In this context, we determined to further explore the utility of the 3,5-dimethyl-1*H*-pyrazole-1-carbodithioates as RAFT agents by examining the effect of introducing a halogen substituent at the 4-position of the pyrazole ring 'Z' group (Fig. 2). It was anticipated that the presence of an electron-withdrawing substituent at this position would reduce the availability of the nitrogen lone pair to donate into the RAFT agent thiocarbonyl group thereby enhancing its reactivity. In particular, we explore the properties of the 4-chloro derivative (**5**) and the 4-bromo derivative (**6**) and their ability to control MMA polymerization. The homo- and copolymerization of monosubstituted MAMs (*N*,*N*-dimethylacrylamide (DMAm), methyl acrylate (MA) and styrene (St)) and VAc (a LAM) and the utility of **5** and **6** in block copolymer synthesis by sequential monomer addition are also examined. Finally we provide a theoretical basis for understanding the enhanced activity of the chlorinated derivative *versus* the parent compound by way of molecular orbital calculations.

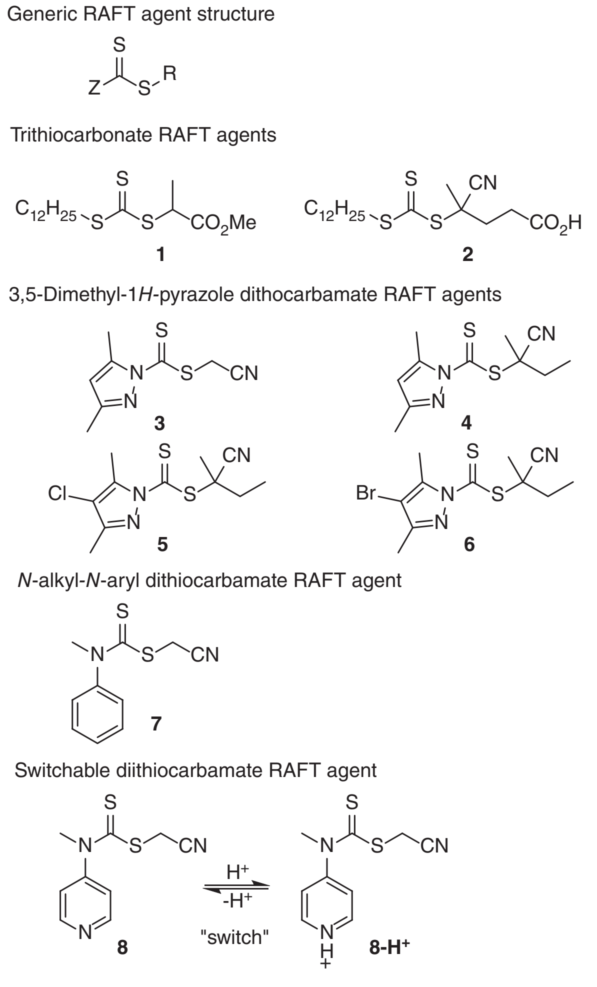


Figure 2. RAFT agents. Structures of a generic RAFT agent, of trithiocarbonates (**1** and **2**), of 3,5-dimethyl-1*H*-pyrazole-1-carbodithioates (**3** and **4**), of 4-halogeno-3,5-dimethyl-1*H*-pyrazole-1-carbodithioates (**5** and **6**), of *N*-alkyl-*N*-aryldithiocarbamate (**7**) and of switchable dithiocarbamate (**8/8-H**$^+$).

RESULTS AND DISCUSSION

In order to provide good control, in particular low *Đ*, it is important that the 'R' group of the initial RAFT agent (Fig. 2) is a similar or better homolytic leaving group than the propagating radical and that R$^•$ is a good initiating radical.[11,26] We have shown that tertiary cyanoalkyl radicals, such as the 2-cyano-2-butyl radical, are a good choice in this context for the case of MMA polymerization.[28] 2-Cyano-2-butyl 4-chloro- (**5**) and 4-bromo-3,5-dimethyl-1*H*-pyrazole-1-carbodithioate (**6**) are readily prepared in a manner similar to that described for the parent, non-halogen-substituted, RAFT agent (**4**).[24] 4-Chloro- and 4-bromo-3,5-dimethylpyrazoles, prepared from 3,5-dimethylpyrazole by halogenation with *N*-chloro- or *N*-bromosuccinimide, respectively,[29] were used as starting points for the syntheses. Generation of the corresponding bis(thioacyl)

Table 1. RAFT homopolymerizations in presence of **5** and **6**[a]

Entry	Monomer	[Monomer] (mol L^{-1})	RAFT agent	[RAFT] (mol L^{-1})	[ACHN][b] (mol L^{-1})	Solvent[b]	Time[a] (h)	Conv. (%)	M_n[c]	M_n(calc)[d] (g mol^{-1})	$Đ$[c]	Ref.[e]
1	DMAm	3.0	**5**	0.03	0.006	CH_3CN	1	99	12200	9696	1.07	
2	DMAm	3.0	**5**	0.03	0.003	CH_3CN	1	99	10600	9885	1.08	
3	DMAm	3.0	**5**	0.03	0.0006	CH_3CN	1	92	9700	9351	1.07	
4	DMAm	3.0	**6**	0.03	0.006	CH_3CN	1	99	11700	9761	1.06	
5	DMAm	3.0	**6**	0.03	0.003	CH_3CN	1	99	11700	9950	1.06	
6	DMAm	3.0	**6**	0.03	0.0006	CH_3CN	1	87	9800	8921	1.07	
7	DMAm	3.0	**4**	0.03	0.003	CH_3CN	1	99	11200	9871	1.08	24
8	DMAm	3.0	**7**	0.03	0.006	CH_3CN	1	99	12800	9651	1.65	24
9	DMAm	3.0	**1**	0.03	0.006	CH_3CN	1	98	10700	9698	1.07	24
10	MA	3.0	**5**	0.03	0.003	CH_3CN	1.5	79	8000	6878	1.14	
11	MA	3.0	**5**	0.03	0.0006	CH_3CN	4	73	7600	6484	1.10	
12	MA	3.0	**6**	0.03	0.0006	CH_3CN	4	60	6900	5441	1.10	
13	MA	3.0	**6**	0.03	0.003	CH_3CN	1.5	79	8100	6942	1.14	
14	MA	3.0	**4**	0.03	0.003	CH_3CN	1	83	7200	7252	1.08	24
15	MA	3.0	**7**	0.03	0.006	CH_3CN	1	88	13400	7497	1.96	24
16	MA	3.0	**1**	0.03	0.006	CH_3CN	1	81	6400	7060	1.06	24
17	St	3.5	**5**	0.0525	0.00525	Toluene	48	52	5000	3642	1.07	
18	St	3.5	**6**	0.0525	0.00525	Toluene	48	49	5500	3512	1.08	
19	St	8.7	**5**	0.13	0	Bulk[f]	24 (110 °C)	85	6900	6192	1.06	
20	St	8.7	**2**	0.13	0	Bulk[f]	24 (110 °C)	92	6800	6816	1.09	
21	MMA	3.5	**4**	0.0263	0.0053	CH_3CN	4	70	14400	8182	1.56	
22	MMA	3.5	**5**	0.0263	0.0053	CH_3CN	4	72	12600	8423	1.34	
23	MMA	3.5	**6**	0.0263	0.0053	CH_3CN	4	79	11500	9280	1.29	
24	MMA	6.55	**4**	0.0495	0.0018	CH_3CN	6 (90 °C)	74	14100[g]	9884	1.55[g]	24
25	MMA	6.55	**5**	0.0495	0.0018	CH_3CN	6 (90 °C)	75	12500	10029	1.43	
26	MMA	6.55	**6**	0.0495	0.0018	CH_3CN	6 (90 °C)	76	12400	10294	1.32	
27	VAc	3.0	**5**	0.048	0.012	EtOAc	48	51	3700	2602	1.17	
28	VAc	3.0	**5**	0.048	0.012	EtOAc	24	43	2500	2236	1.09	
29	VAc	3.0	**6**	0.048	0.012	EtOAc	24	28	1600	1614	1.05	
30	VAc	3.0	**3**	0.048	0.012	EtOAc	12	62	5000	3056	1.29	24
31	VAc	3.0	**4**	0.048	0.012	EtOAc	48	57	4600	2862	1.17	24
32	VAc	3.0	**7**	0.048	0.012	EtOAc	2	85	6200	4426	1.18	24

[a] All experiments were conducted with microwave heating at 100 °C unless otherwise indicated. All concentrations are based on the mass or volume of material used at 22 °C and do not take into account volume of mixing effects.

[b] ACHN = 1,1′-azobis(1-cyanocyclohexane), EtOAc = ethyl acetate.

[c] SEC (DMAc) number-average molar mass in poly(MMA) equivalents rounded to nearest 100.

[d] Calculated molar mass estimated using the relationship $M_n(\text{calc}) = ([\text{M}] \times \text{conv.})/([\text{RAFT}] + (d \times 0.7 \times [\text{ACHN}](1 - \exp(-k_d t))) \times M_{\text{monomer}} + M_{\text{RAFT}})$, where d is assumed to be 1.0 for DMAm, MA, St and VAc, and 1.67 for MMA, k_d is the rate constant for decomposition of the initiator (9.59×10^{-5} s^{-1} at 100 °C and 2.54×10^{-5} s^{-1} at 90 °C), t is the reaction time and M_{monomer} and M_{RAFT} are the molar mass of the monomer and the RAFT agent, respectively.[10,42]

[e] Experiments from present study unless indicated otherwise.

[f] Experiments with bulk monomer, no allowance in *Mn*(calc) for thermal initiation.

[g] SEC (tetrahydrofuran).

disulfides and their radical-induced decomposition,[30] by treatment with azobis(2-cyano-2-butane) as a source of 2-cyano-2-butyl radicals, provided acceptable (*ca* 75%) yields of the dithiocarbamate RAFT agents **5** and **6**.

To assess the effect of halogen substitution on the pyrazole ring, the halogenated RAFT agents **5** and **6** were examined in polymerizations of DMAm, MA, St, MMA and VAc. Most polymerizations were carried out under microwave conditions at 100 °C using 1,1′-azobis(1-cyanocyclohexane) (ACHN) as thermal initiator. As in previous work,[24] conditions for the polymerizations were chosen to provide rapid polymerization of monomers as is required for polymerization in continuous flow.[18] We demonstrated in the earlier study that there is no 'microwave effect' in these RAFT polymerizations.[24,31] Results are summarized in Table 1 (homopolymerizations), Table 2 (binary copolymerizations) and Table 3 (block copolymers).

The activities of the RAFT agents **5** and **6** in mediating polymerizations of monosubstituted MAMs, namely DMAm, MA and styrene, appear generally similar to those observed for the corresponding trithiocarbonates, and **4**, with $Đ < 1.1$ being achieved for the conditions used (Table 1). Our previous paper[24] contains comparative data.

As with **4**, the halogenated RAFT agents **5** and **6** also provide control over VAc polymerizations with $Đ < 1.2$ being obtained (Table 1, entries 27–29). This finding is in marked contrast to trithiocarbonates, which, under most circumstances, completely inhibit polymerization of VAc and other LAMs.[11] While significant retardation with VAc is observed compared to RAFT-free

Table 2. RAFT copolymerizations in presence of **5** and **6**[a]

Entry	Monomer 1/ monomer2	[Monomer] (mol L^{-1})	RAFT agent	[RAFT] (mol L^{-1})	[ACHN][b] (mol L^{-1})	Solvent	Time (h)	Conv.[c] (%)	M_n[d]	M_n(calc)[e] (g mol^{-1})	$Đ$
1	DMAm/MA	1.5/1.5	**5**	0.03	0.003	CH$_3$CN	1	90/89	8300	8338	1.16
2	DMAm/MA	1.5/1.5	**6**	0.03	0.003	CH$_3$CN	1	90/87	9200	8253	1.13
3	MMA/DMAm	1.5/1.5	**5**	0.03	0.003	CH$_3$CN	4	91/72	8600	8054	1.19
4	MMA/DMAm	1.5/1.5	**6**	0.03	0.003	CH$_3$CN	4	89/61	8000	6589	1.19
5	MMA/St	1.5/1.5	**5**	0.03	0.006	Toluene	12	66/69	6000	6409	1.19
6	MMA/St	1.5/1.5	**6**	0.03	0.006	Toluene	12	43/40	3800	3974	1.19
7	DMAm/VAc	1.5/1.5	**5**	0.03	0.003	CH$_3$CN	12	99/48	7000	6760	1.18
8	DMAm/VAc	1.5/1.5	**6**	0.03	0.003	CH$_3$CN	12	99/26	7100	5856	1.18

[a] All experiments were conducted with microwave heating at 100 °C. All concentrations are based on the mass or volume of material used at 22 °C and do not take into account volume of mixing effects.
[b] ACHN = 1,1′-azobis(1-cyanocyclohexane).
[c] Conversion of monomer 1/monomer 2.
[d] SEC (DMAc) number-average molar mass in poly(MMA) equivalents rounded to nearest 100.
[e] $M_n(\text{calc}) = (([M1] \times \text{conv1} \times M_{\text{monomer1}}) + ([M2] \times \text{conv2} \times M_{\text{monomer2}}))/([\text{RAFT}] + (d \times 0.7 \times [\text{ACHN}](1 - \exp(k_d t))) + M_{\text{RAFT}})$, where [M1] is the concentration of monomer 1, [M2] is the concentration of monomer 2, conv1 and conv2 are the respective total monomer conversions, d is assumed to be 1.0, k_d is the rate constant for decomposition of the initiator (9.59×10^{-5} s^{-1} at 100 °C), t is the reaction time and $M_{\text{monomer}n}$ and M_{RAFT} are the molar masses of the monomers and the RAFT agent, respectively.[10,42]

Table 3. Block copolymers prepared with **5**[a]

Monomer block 1	Monomer block 2	[M] (mol L^{-1})	RAFT agent	[RAFT] (mol L^{-1})	[ACHN][b] (mol L^{-1})	Solvent	Time (h)	Conv. (%)[c]	M_n[d]	M_n(calc)[e] (g mol^{-1})	$Đ$
DMAm*		1.5	**5**	0.03	0.003	CH$_3$CN	0.75	92/>99	5100	4800	1.05
	MA	1.5[f]			0.003[d]		2	91	9500	9160	1.25
DMAm*		1.5	**5**	0.03	0.003	CH$_3$CN	0.75	90/98	5800	5170	1.08
	VAc	1.5[f]			0.003[d]		12	35	8500	7730	1.17

[a] All experiments were conducted with microwave heating at 100 °C. Block copolymers were prepared as quasi-blocks by addition of the second monomer and additional initiator and solvent to the polymerization reaction mixture without isolation of the first block. All concentrations are based on the mass or volume of material used at 22 °C and do not take into account volume of mixing effects.
[b] ACHN = 1,1′-azobis(1-cyanocyclohexane).
[c] Conversion of the monomer indicated. Two numbers are provided for monomer 1 conversion, these are: monomer 1 consumed in formation of block 1/total monomer 1 consumed during formation of blocks 1 and 2.
[d] SEC (DMAc) number-average molar mass in poly(MMA) equivalents rounded to nearest 100.
[e] Calculated molar mass estimated using the relationship $M_n(\text{calc}) = ([M] \times \text{conv})/([\text{RAFT}] + (d \times 0.7 \times [\text{ACHN}](1 - \exp(k_d t))) \times M_{\text{monomer}} + M_{\text{RAFT}})$, where [M] is the total monomer concentration, [ACHN] is the initiator concentration (cumulative over both steps in the case of blocks), d is assumed to be 1.0, k_d is the rate constant for decomposition of the initiator (9.59×10^{-5} s^{-1} at 100 °C), t is the total reaction time, M_{monomer} is the monomer molar mass (weighted average for copolymers) and M_{RAFT} is the molar mass of the RAFT agent or macro-RAFT.
[f] Amount of monomer or initiator added in synthesis of second block in molar equivalents (not a concentration).

polymerization or the use of *N*-phenyl-*N*-methyldithiocarbamate (**7**) (Table 1, entry 32), good control over molar mass and $Đ$ is, nevertheless, achieved. While the dithiocarbamate **7** provides low $Đ$ with minimal retardation when mediating the polymerization of LAMs, it displays at best poor control over polymerization of MAMs (e.g. DMAm and MA) with $Đ > 1.6$.[24]

As anticipated, the halogen-substituted dithiocarbamates **5** and **6** gave improved control over MMA polymerization with molar masses at high monomer conversion being closer to the expected M_n(calc) and $Đ < 1.4$ (Table 1, entries 22, 23, 25, 26). These results can be contrasted with those obtained with the parent RAFT agent **4**, where molar masses were significantly higher than expected and $Đ > 1.5$ (Table 1, entries 21, 24). The effect can be better appreciated by examining the molar mass distributions shown in Fig. 3. These are consistent with C_{tr} of RAFT agents **5** and **6** being significantly higher than that of **4**. Based on the observed value of $Đ$,[24] C_{tr} for **6**, **5** and **4** was estimated as 5.6, 5.4 and 3.4, respectively. Note that these C_{tr} values are strongly dependent on the precision of the gel permeation chromatography measurements of $Đ$, and do not allow for column plate count, band broadening or other effects. The difference in activity between **5** and **6** is not regarded as significant. The evolution of the molar mass distributions as a function of monomer conversion with **4**, **5** and **6** (provided in the supporting information) is consistent with this assessment.

The chloro- (**5**) and bromo-substituted (**6**) pyrazoles offer generally similar scope and control over polymerization; slightly lower conversions were observed with **6** under the same reactions conditions for MAMs (Table 1). More pronounced retardation was seen with **6** for VAc (Table 1, entry 29). Observations of greater retardation with more active RAFT agents are not unusual and this can often be linked with higher stability for the intermediate formed by addition to the RAFT agent, and the greater likelihood of that species undergoing side reactions.[11,32] It can be noted that the tertiary cyanoalkyl R group of **4**–**6** is not ideal for VAc polymerization, in that the rate of addition of the tertiary cyanoalkyl formed from the RAFT agent is likely to be less than the monomer propagation

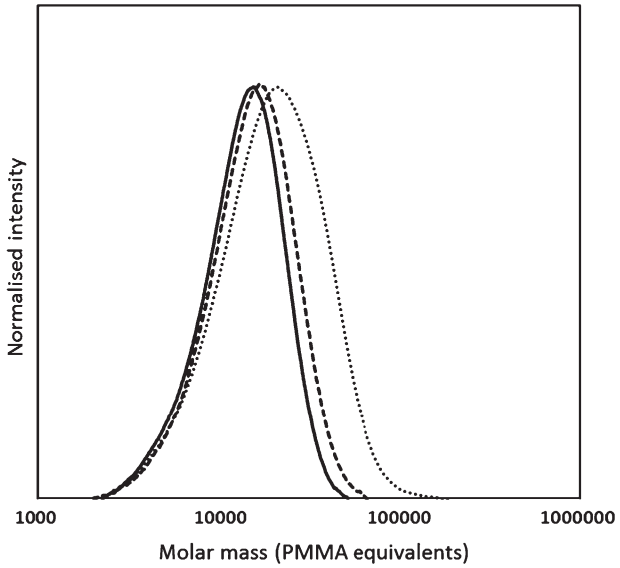


Figure 3. Molar mass distributions of poly(MMA) prepared with RAFT agents **4** (dotted curve), **5** (dashed curve) or **6** (solid curve) at 100 °C under microwave heating with [MMA] = 3.5 mol L^{-1}, [RAFT] = 0.0263 mol L^{-1} and [ACHN] = 0.0058 mol L^{-1}. Examples correspond to entries 21–23 of Table 1.

rate constant.[28] This also is a potential cause of retardation and slow utilization of the RAFT agent with each of **4**–**6**.[11] However, at this stage, given that **6** appears to be, at most, only slightly more active than **5**, we have no unequivocal explanation for the observation of greater retardation.

The synthesis of several copolymers in the presence of **5** and **6** was also investigated (Table 2). Good molar mass and *Đ* control was observed in each case. These results are similar to those reported with **4**.[24] RAFT copolymerizations are expected to provide gradient copolymers.[24] Reactivity ratios for DMA and VAc are not available. Those for *N*-acryloylpiperidine (NAPi) and VAc, which may be similar, are $r_{\mathrm{NAPi}} = 8.26$ and $r_{\mathrm{VAc}} = 0.0$.[33] These values indicate that DMAm should be rapidly consumed during the early stages of copolymerization. As was observed in VAc homopolymerization (Table 1, entry 29), reduced conversion of VAc was also observed in the preparation of poly(VAc-*grad*-DMAm) when using bromo-substituted RAFT agent **6** (Table 2, entry 8) with respect that seen in copolymerizations using either the parent **4**[24] or the choro-substituted RAFT agent **5** (Table 2, entry 7).

RAFT agent **5** was also used in the synthesis of poly(DMAm)-*block*-poly(MA) and importantly poly(DMAm)-*block*-poly(VAc) polymers (Table 3). As in the previous study,[24] the block copolymers were prepared as ‘quasi’ blocks,[34–36] with the first DMAm block being taken to around 90% monomer conversion and the macro-RAFT agent not isolated before proceeding with the preparation of the second block. The structures are, therefore, more accurately described as poly(DMAm)-*block*-poly(DMAm-*grad*-MA) and poly(DMAm)-*block*-poly(DMAm-*grad*-VAc), respectively. Low *Đ* was observed (supporting information and Table 3). The reactivity ratios will ensure that the length of the gradient section is short.

SEC traces showing the evolution of the molar mass distribution in the preparation of poly(DMAm)-*block*-poly(MA) and poly(DMAm)-*block*-poly(VAc) with **5** are provided in Fig. 4. For poly(DMAm)-*block*-poly(MA) these show a progressive shift to high molar mass as expected. For MA conversions greater than *ca* 90% the development of a high-molar-mass shoulder is observed along with the appearance of a low-molar-mass peak that tails to lower molar mass. This is particularly evident with UV detection at 310 nm. At 310 nm the monomer and the polymer (less end group) should be transparent and only the RAFT end groups absorb. It is clear that between 85 and 95% monomer conversion approximately half the RAFT end groups are lost from the block and reappear in what is most likely a low-molar-mass poly(MA) homopolymer. The high-molar-mass shoulder also contains RAFT end groups so we conclude it is not a termination product but most likely a graft polymer. Possible mechanisms for the formation of graft copolymers have been discussed previously for the case of trithiocarbonate-mediated RAFT polymerization.[37] The chemistry as described there[37] is not dependent on the particular RAFT agent but is dependent on the initiator and its excess. The use of strategies recently exploited in multiblock copolymer synthesis may be applicable here.[38] Another possible method of mitigating these complications is to generate radicals directly from the RAFT agent, for example, by photolysis.[39,40] Xu *et al.*[41] have recently demonstrated that photolysis (PET-RAFT) may be applied to achieve very high yield and end-group fidelity in RAFT single unit monomer insertion. These processes are being examined in the context of block copolymer synthesis and will be reported on at a later date.

For poly(DMAm)-*block*-poly(VAc), a shift of the molar mass distribution to higher molar mass was again observed indicating that a block copolymer was synthesized (Table 3). However, the quality of the block copolymer was negatively impacted by the retardation inherent in VAc polymerization with the pyrazole RAFT agent **5**. To put these results in perspective, a block copolymer was also synthesized under experimental conditions similar those used with the switchable RAFT agent **8**.[21] The end group was in unswitched or neutral form for the synthesis of the poly(VAc) block. Substantially less retardation was evident and poly(DMAm) (M_n (SEC) = 10 000, $M_w/M_n = 1.17$) previously prepared with $\mathbf{8H^+}$ was converted to poly(DMAm)-*block*-poly(VAc) (M_n (SEC) = 20 100, $M_w/M_n = 1.15$) after a reaction time of 6 h (65% conversion of VAc).[21]

Under similar conditions, poly(DMAm) prepared with **5** (M_n (SEC) = 6050, $M_w/M_n = 1.10$) was converted to poly(DMAm)-*block*-poly(VAc). After 6 h, there was 17% conversion of VAc (M_n (SEC) = 7200, $M_w/M_n = 1.15$) and after 16 h, 22% conversion of VAc (M_n (SEC) = 8600, $M_w/M_n = 1.23$). The SEC traces (Fig. 5) show the shift of the molar mass distribution and the development of a high-molar-mass shoulder. The shoulder is markedly diminished in the trace with UV detection suggesting that it comprises largely the termination product. The tail in the molar mass distribution to lower values can be attributed to initiator-derived chains.

We conclude that while poly(DMAm)-*block*-poly(VAc) can be prepared with the pyrazole RAFT agents, there are significant constraints on the process. As above, a possible method of avoiding complications associated with initiator-derived chains may be to generate radicals directly from the RAFT agent. However, this would not avoid the issue of retardation.

Computational results

While the relative activity of the dithiocarbamates introduced in this study can be ascribed to the electronic effects produced by the introduced halogen atoms, the reason for these differences requires further investigation. In simple terms, however, consideration of electron delocalization, as represented by the various canonical structures shown in Fig. 6, may be instructive. Whilst resonance between II and IV stabilizes the C=S double bond and lowers its reactivity, cross-conjugation with I and III interferes with this

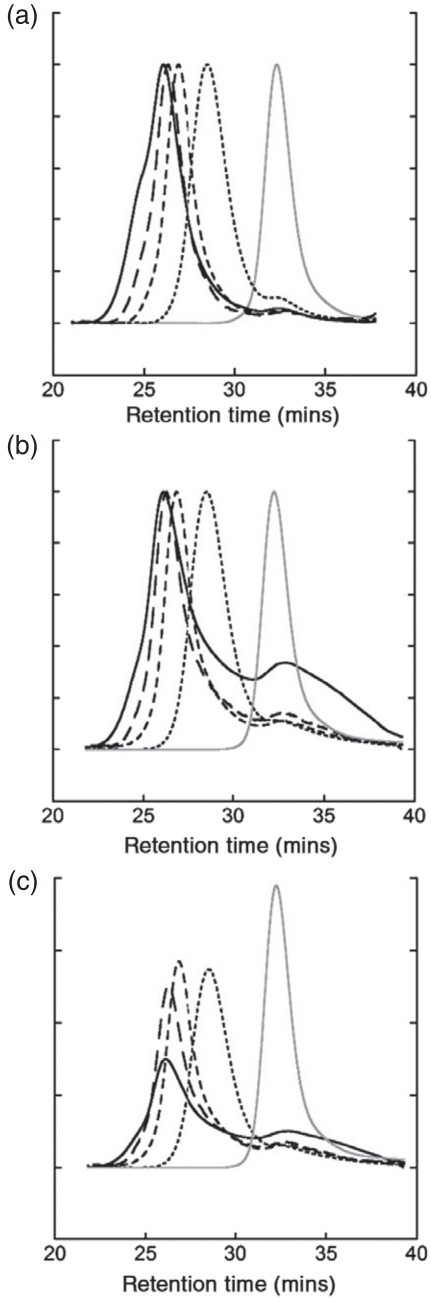


Figure 4. SEC chromatograms (DMAc) of poly(DMAm)-*block*-poly(MA) prepared with RAFT agent **5** at 100 °C under microwave heating with [MA] = 3.5 mol L^{-1}, [poly(DMAm) macro-RAFT] = 0.0263 mol L^{-1} and [ACHN] = 0.0058 mol L^{-1}. SEC traces were obtained with (a) refractive index detection normalized to largest peak, (b) UV detection at 310 nm normalized to largest peak and (c) UV detection at 310 nm normalized to RAFT end groups (intensity = slice area/sum of all slice areas), after 0 (solid grey curve), 5 (dotted curve), 15 (short-dashed curve), 30 (long-dashed curve) or 60 min (solid black curve) polymerization time.

by tying up the nitrogen lone pair. A halogen would be expected to further stabilize the cross-conjugation contributors and, in doing so, further activate the double bond towards radical addition. Such cross-conjugation does not occur in the case of the non-pyrazole RAFT agent **7**, which thus has a more stable C=S bond that is less reactive towards radical addition and is suitable only for LAMs such as VAc monomers that generate more reactive propagating radicals.

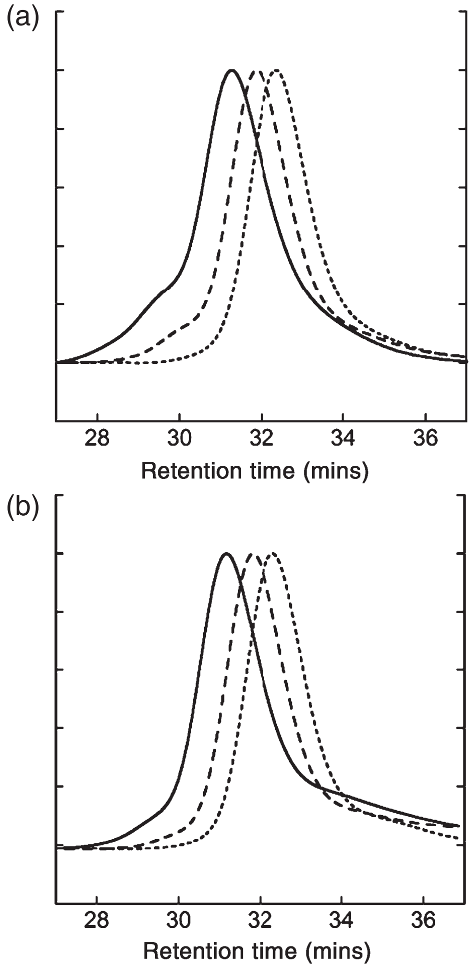


Figure 5. SEC chromatograms (DMAc) of poly(DMAm)-*block*-poly(VAc) prepared with RAFT agent **5** at 100 °C under microwave heating with [VAc] = 8.0 mol L^{-1}, [poly(DMAm) macro-RAFT] = 0.052 mol L^{-1} and [ACHN] = 0.0045 mol L^{-1} after 0 (short-dashed curve), 6 (long-dashed curve) and 16 h (solid curve). SEC traces were obtained with (a) refractive index detection normalized to largest peak and (b) UV detection at 310 nm normalized to largest peak.

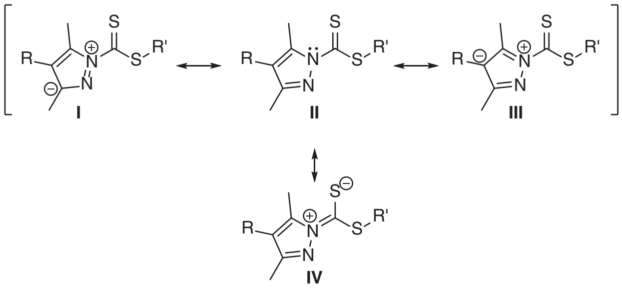
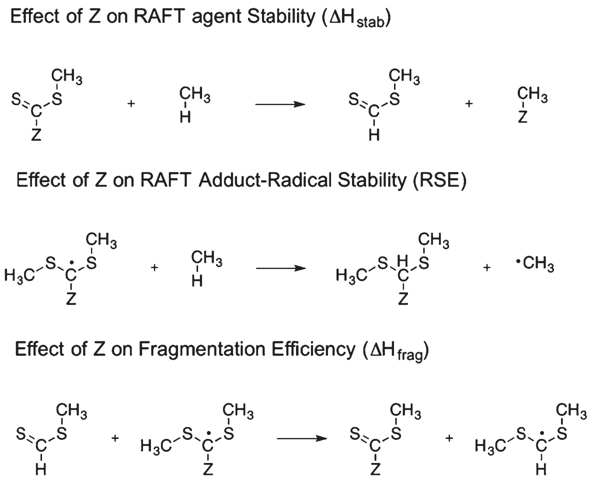


Figure 6. Canonical forms of 3,5-dimethylpyrazole dithiocarbamates.

Density functional theory calculations have recently been carried out for similar 3,5-dimethylpyrazole compounds and their associated metal complexes.[43,44] In the present work, we use higher-level *ab initio* molecular orbital calculations to assess qualitatively the relative reactivities of pyrazole and non-pyrazole dithiocarbamates. We have used these methods to calculate a number of thermodynamic descriptors, including RAFT agent stability (ΔH_{stab}), the radical stabilization energy (RSE) of the adduct



Scheme 1. Definitions of RAFT agent stability (ΔH_{stab}), RAFT adduct RSE and fragmentation efficiency (ΔH_{frag}).

formed by radical addition to the RAFT agent and the fragmentation efficiency of that species (ΔH_{frag}). These three descriptors were first introduced to provide a simple semi-quantitative means of assessing the likely kinetic behaviour of any new RAFT agent relative to known compounds, prior to undertaking experimental work and/or more extensive *ab initio* studies.[45,46] The definitions of these terms are provided in Scheme 1, and are explained in more detail below. Geometries were optimized using M06-2X/6-31 + G(d),[47] while improved energy calculations were carried out with the high-level composite *ab initio* method using G3(MP2)-RAD,[28] which has previously been benchmarked for similar reactions.[48] Standard *ab initio* and density functional theory calculations were carried out using the Gaussian 09[49] and Molpro 2015[50] software packages. All geometries and total energies are provided in the supporting information.

The descriptor ΔH_{frag} provides a measure of the effect of the RAFT agent Z group on the enthalpy of the fragmentation reaction, relative to a reference compound with Z = H. The more exothermic the value, the more easily a given leaving group will fragment. Calculated values for known RAFT agents are shown in Fig. 7 and span a range of nearly 100 kJ mol^{-1}. The most exothermic values are associated with the xanthates and *N*,*N*-dialkyldithiocarbamates, which are capable of promoting fragmentation of most (if not all) propagating radicals. The most endothermic values are associated with RAFT agents containing π-acceptor Z groups such as phenyl and cyano. These Z substituents retard fragmentation of the RAFT adduct radical. As a consequence, the corresponding RAFT agents are only suitable for polymerizations of St, MMA or other MAMs which provide more stabilized propagating radicals that are better homolytic leaving groups.

The enthalpy of fragmentation for a fixed leaving group depends on how the Z group stabilizes the RAFT agent and the RAFT adduct radical. Decoupling these effects is important in RAFT agent design as it is the stabilization of the RAFT agent, rather than the adduct radical, that has the most dramatic impact on the kinetics of radical addition. The descriptor ΔH_{stab} is designed to assess the effect of the Z group on the stability of the C=S moiety of the RAFT agent. The standard RSE provides a measure of the stability of the RAFT adduct radical. In each case, the radical or RAFT agent is compared with a corresponding reference compound, and the reaction is then balanced using simple hydrocarbons. The implicit assumption is that the effects of substituents on simple hydrocarbons are substantially smaller than those on the π-group or unpaired electron in the RAFT agent and RAFT adduct radical, respectively, where resonance and other interactions are possible.

Whilst ΔH_{stab} is a simplified thermodynamic quantity, previous studies[25] have shown that it is strongly correlated with the reactivity of the RAFT agent towards radical addition. Less reactive RAFT agents such as xanthates and *N*,*N*-dialkyldithiocarbamates have ΔH_{stab} values of the order of 80–100 kJ mol^{-1}. The more active trithiocarbonates and dithiobenzoates have much lower values (*ca* 60 and *ca* 40 kJ mol^{-1}, respectively).[31] As a rule of thumb, RAFT agents with values comparable to xanthates and *N*,*N*-dialkyldithiocarbamates are only suitable for controlling polymerizations of LAMs (e.g. VAc), which generate more reactive propagating radicals, while RAFT agents such as trithiocarbonates and dithioesters are sufficiently reactive towards radical addition to enable control the polymerization of most types of monomer.

To assess the RAFT agents of the present study, values of their ΔH_{stab}, RSE and ΔH_{frag} descriptors were calculated and are presented in Table 4. To place them in context, Fig. 7 shows these descriptor alongside published values[45,46] for other Z groups. In the case of the ΔH_{frag} and ΔH_{stab} values, a dividing line is drawn between the values of typical trithiocarbonates and dithioesters and those of typical xanthates and *N*,*N*-dialkyldithiocarbamates. As discussed above, the former are most suitable for MAMs because the substituents convey appropriate ΔH_{stab} values but ΔH_{frag} values that are not exothermic enough to allow facile fragmentation of the propagating radicals. The latter are only suitable for LAMs because they have exothermic ΔH_{frag} values but ΔH_{stab} values that are too high to allow control over polymerization of MAMs. The only RAFT agent previously identified with the potential to be universal, having compatible ΔH_{frag} and ΔH_{stab} values for both stabilized and unstabilized propagating radicals, is the fluorodithioformate with Z = F – note that the universality of this RAFT has not been fully verified experimentally.[51,52] The predicted properties of fluorodithioformate can be attributed to a relatively low RAFT adduct RSE value (Scheme 1). The fluorine substituent is predicted to promote fragmentation without stabilizing the RAFT agent. Use of a single agent to control stable and unstable monomers has also been achieved through pH switching of an aromatic amine Z group in which the deprotonated form is suitable for control of LAMs and the protonated form is suitable for MAMs (e.g. **8**, **8-H**$^+$).[17–23]

Based on the simplified descriptors, the dithiocarbamate RAFT agent with Z = N(CH$_3$)Ph produces a RAFT agent with high ΔH_{stab}, and is, therefore, expected to be inactive for monomers with stabilized propagating radicals (MAMs), but suitable for monomers with less stabilized propagating radicals (LAMs). This is attributed to the nitrogen lone pair undergoing resonance with the thiocarbonyl double bond. In contrast, the pyrazole-based RAFT agents have a lower ΔH_{stab}, and are thus more activated towards radical addition, but their adduct radicals undergo fragmentation less easily. As a result, they are more suited to monomers which generate less stabilized propagating radicals (i.e. LAMs). However the pyrazole RAFT agents, and in particular the 4-chloro-3,5-dimethyl-1*H*-pyrazole substituted RAFT agent **5**, are very close to the cut-off between the LAMs and MAMs, and thus likely to be reasonably suitable for both, as shown here experimentally. The reason for the performance of the 4-chloro-3,5-dimethyl-1*H*-pyrazole RAFT agent **5** is that, just as with the fluorodithioformate RAFT agent, fragmentation is

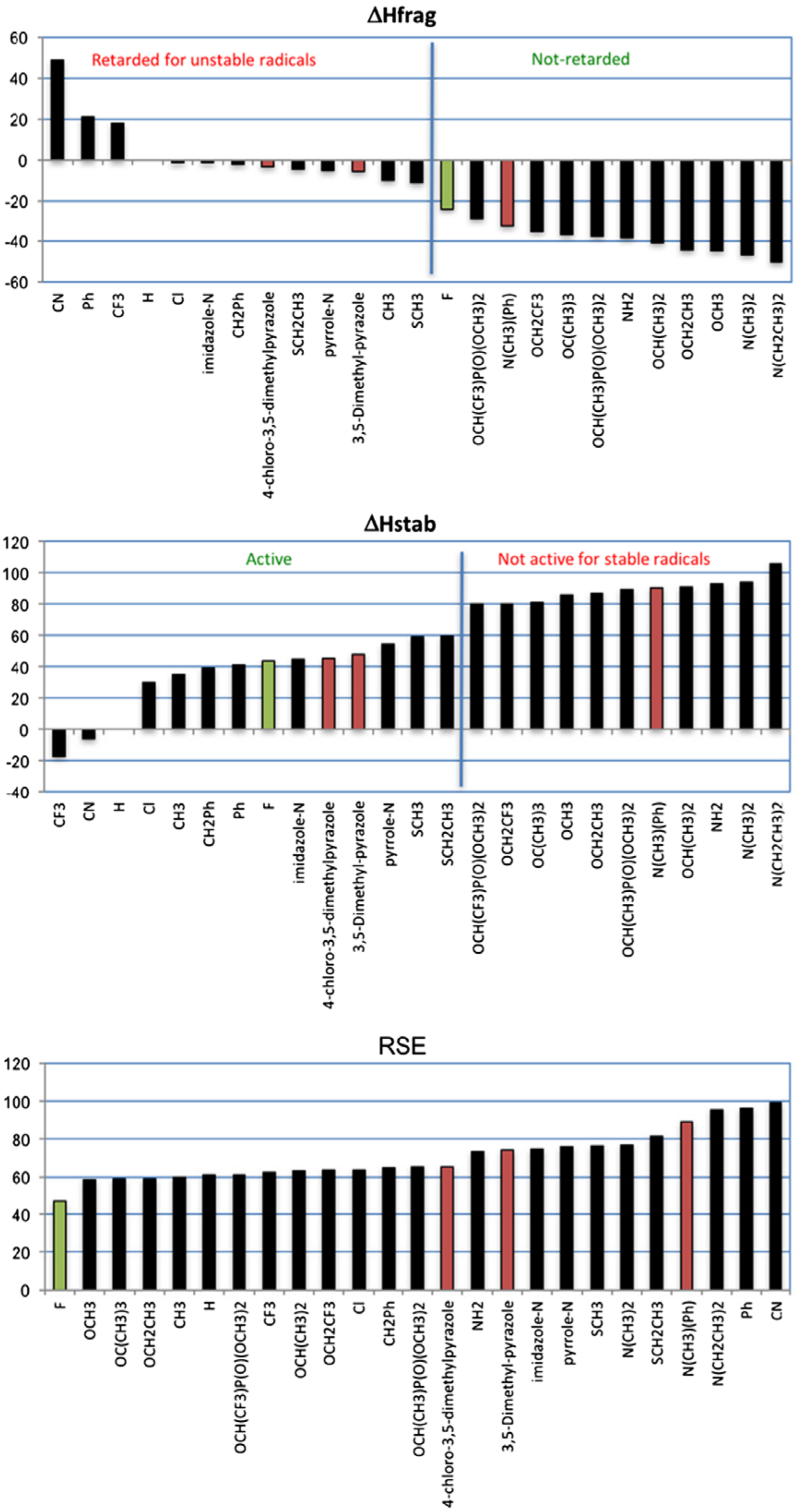


Figure 7. Values of RSE, ΔH_{stab} and ΔH_{frag} (kJ mol^{-1}) for RAFT agents in the present study, and reference values for other RAFT agents.[45,46]

favoured by the RAFT adduct radical being relatively unstable. The halogen substituent interferes with the ability of the pyrazole ring to stabilize the RAFT adduct radical. Note that trithiocarbonates have similar ΔH_{frag} values, but much lower ΔH_{stab} values, and hence they are only suited for mediating polymerization of MAMs.

CONCLUSIONS

The 4-halogeno-3,5-dimethyl-1*H*-pyrazole-1-carbodithioates **5** and **6** have widespread applicability in RAFT polymerization with the ability to control polymerizations of both MAMs (DMAm, MA, St and MMA) and a LAM (VAc). Compound **5** provides poly(MMA)

Table 4. Values of ΔH_{stab}, RSE and ΔH_{frag} (0 K) for the RAFT agents in the present work

Z group	ΔH_{stab} (kJ mol^{-1})	RSE (kJ mol^{-1})	ΔH_{frag} (kJ mol^{-1})
3,5-Dimethylpyrazole	47.9	74.1	−5.5
4-Chloro-3,5-dimethyl-1*H*-pyrazole	45.0	65.5	−3.2
N(CH_3)Ph	90.6	89.1	−32.7

of relatively low *Đ* (≤1.4 at high conversion), something that was not achieved with the parent RAFT agent **4**. The experimental findings are supported by high-level molecular orbital calculations, which indicate that of 3,5-dimethylpyrazole-based RAFT agents possess properties suitable for controlling the polymerization of both MAMs and LAMs.

In particular, the RAFT agent **5** stands out as being broadly applicable providing reasonable control over the polymerization and copolymerization of a wide range of monomers. While switchable RAFT agents can be seen to provide significantly better control (lower *Đ* for 1,1-disubsituted MAMs, less retardation with LAMs), the 3,5-dimethyl-1*H*-pyrazole-1-carbodithioates have important benefits over the switchable RAFT agents in terms of ease of synthesis and simplicity in application (since there is no requirement for switching when used for MAMs *versus* LAMs). The 3,5-dimethyl-1*H*-pyrazole-1-carbodithioates can also be seen as appropriate replacements for trithiocarbonates in polymerizations of monosubstituted MAMs. They offer similar control and, while they have low molar mass, they possess little odour and polymers formed with their use do not develop odour on storage under ambient conditions. These pyrazole-based RAFT agents are currently being explored in a range of applications to further establish their scope and versatility.

EXPERIMENTAL

Materials and methods

The RAFT agents were prepared as indicated below or were obtained from Boron Molecular.[53] 3,5-Dimethylpyrazole was obtained from Fluka and *N*-chlorosuccinimde and *N*-bromosuccinimide were obtained from Aldrich. Monomers (MA, DMAm, St, MMA, VAc) were obtained from Aldrich and were treated with inhibitor remover (Aldrich) and flash-distilled prior to use. ACHN (Vazo88™) was obtained from DuPont.

SEC was performed using a Shimadzu instrument equipped with a CMB-20A controller system, a SIL-20A HT autosampler, a LC-20AT tandem pump system, a DGU-20A degasser unit, a CTO-20 AC column oven, a RDI-10A refractive index (RI) detector and four Styragel (Waters) columns (HT2, HT3, HT4 and HT5). *N*,*N*-dimethylacetamide (DMAc; containing 4.3 g L^{-1} LiBr) was used as eluent at a flow rate of 1 mL min^{-1}. The column temperature was set to 80 °C and the refractive index detector temperature was set to 40 °C. The SEC instrument was calibrated with low-*Đ* poly(MMA) standards, and molar masses are reported as poly(MMA) equivalents. M_n and *Đ* were evaluated using Shimadzu software (LabSolutions version 5.63). A third-order polynomial was used to fit the log(molar mass) *versus* time calibration curve, which was approximately linear across the molar mass range of interest. NMR spectra were obtained with a Bruker Avance 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C). High-resolution mass spectra were obtained with a Thermo Scientific Q Exactive FTMS employing ASAP/APCI probes. Microwave irradiation experiments were carried out using a Biotage Initiator Sixty microwave system.

RAFT agent synthesis and characterization

4-Chloro-3,5-dimethylpyrazole

Prepared according to a literature procedure[29] (yield = 97%). ^{1}H NMR ($CDCl_3$, 400 MHz; δ, ppm): 2.22 (s, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz; δ, ppm): 10.5, 107.9, 141.1, in accordance with the literature.[29]

4-Bromo-3,5-dimethylpyrazole

Prepared according to a literature procedure[29] (yield = 94%). ^{1}H NMR ($CDCl_3$, 400 MHz; δ, ppm): 2.22 (s, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz; δ, ppm): 11.4, 94.2, 142.8, in accordance with the literature.[29]

2-Cyano-2-butyl
*4-chloro-3,5-dimethyl-1*H*-pyrazole-1-carbodithioate (**5**)*

RAFT agent **5** was prepared by radical-induced decomposition of bis(thioacyl)disulfide using a procedure analogous to that described in the literature.[24,54] The product, which crystallized from hot toluene in 73% yield, had a melting point of 73–74 °C. ^{1}H NMR ($CDCl_3$, 400 MHz; δ, ppm): 1.19 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.86 (s, 3H, CH_3), 2.02 (dq, *J* = 7.4, 14.0 Hz, 1H, CH_aCH_3), 2.26 (s, 3H, CH_3), 2.27 (dq, *J* = 7.4, 14.0 Hz, CH_bCH_3), 2.68 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz; δ, ppm): 9.4, 11.8, 15.5, 24.0, 32.3, 46.5, 117.3, 119.7, 140.9, 149.4, 194.4. The full NMR spectra are provided in the supporting information. HRMS (APCI): calcd for $C_{11}H_{15}N_3S_2Cl$ $[M + H]^+$ 288.0390, 290.0361; found 288.0390, 288.0357.

2-Cyano-2-butyl
*4-bromo-3,5-dimethyl-1*H*-pyrazole-1-carbodithioate (**6**)*

RAFT agent **6** was prepared by radical-induced decomposition of the bis(thioacyl)disulfide using a procedure similar to that described in the literature.[24,54] The product, which crystallized from hot toluene in 75% yield, had a melting point of 80–82 °C. ^{1}H NMR ($CDCl_3$, 400 MHz; δ, ppm): 1.20 (t, *J* = 7.4 Hz, 3H, CH_3), 1.86 (s, 3H, CH_3), 2.04 (dq, *J* = 7.5, 14.0 Hz, 1H, CH_aCH_3), 2.25 (dq, *J* = 7.5, 14.0 Hz, 1H, CH_bCH_3), 2.27 (s, 3H, CH_3), 2.70 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz; δ, ppm): 9.4, 12.8, 16.6, 23.9, 32.3, 46.6, 105.0, 119.7, 142.7, 150.6, 194.3. The full NMR spectra are provided in the supporting information. HRMS (APCI): calcd for $C_{11}H_{14}N_3S_2Br$ $[M + H]^+$ 331.9885, 333.9865; found 331.9885, 333.9863.

Polymerizations

*Preparation of poly(MMA) using **4**–**6***

The synthesis of poly(MMA) is detailed in the supporting information.

*Preparation of poly(DMAm) using **5** at 100 °C*

A solution containing DMAm (0.618 mL, 3 mol L^{-1}), ACHN (1.47 mg, 0.003 mol L^{-1}), **5** (17.27 mg, 0.03 mol L^{-1}), trioxane (10 mg, internal standard) and acetonitrile (1.382 mL) was prepared in a microwave vial. The resulting mixture was degassed, sealed and heated at 100 °C by microwave irradiation for 1 h. The volatiles were removed *in vacuo* to give poly(DMAm) at 99% conversion of DMAm (determined by ^{1}H NMR), with M_n of 10 637, *Đ* = 1.08 (Table 1, entry 2).

*Preparation of poly(DMAm)-co-poly(VAc) using **5** at 100 °C*

A solution containing DMAm (0.309 mL, 1.5 mol L^{-1}), VAc (0.277 mL, 1.5 mol L^{-1}), ACHN (1.47 mg, 0.003 mol L^{-1}), **5** (17.27 mg, 0.03 mol L^{-1}), trioxane (10 mg, internal standard) and acetonitrile (1.414 mL) was prepared in a microwave vial. The resulting mixture was degassed, sealed and heated at 100 °C by microwave irradiation for 12 h. The volatiles were removed *in vacuo* to give poly(DMAm-*co*-VAc) at 99% conversion of DMAm and 48% conversion of VAc, with M_n of 7086, $Đ = 1.18$ (Table 2, entry 7).

*Preparation of poly(DMAm)-block-poly(VAc) using **5** at 100 °C*

A solution containing DMAm (0.309 mL, 1.5 mol L^{-1}), ACHN (1.47 mg, 0.003 mol L^{-1}), **5** (17.27 mg, 0.03 mol L^{-1}), trioxane (10 mg, internal standard) and acetonitrile (1.414 mL) was prepared in a microwave vial. The resulting mixture was degassed, sealed and heated at 100 °C by microwave irradiation for 45 min (a sample showed poly(DMAm) at 90% conversion with M_n of 5800, $Đ = 1.05$). The vial cap was removed and VAc (0.277 mL) and ACHN (1.47 mg) were added. The vial was again sealed, degassed and heated at 100 °C for 12 h. The volatiles were removed *in vacuo* to give poly(DMAm)-*block*-poly(VAc) at 99% conversion of DMAm and 31% conversion of VAc, with M_n of 8500, $Đ = 1.24$ (Table 3, entry 2).

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SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

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