Living Free-Radical Polymerization by Reversible Addition−Fragmentation Chain Transfer: The RAFT Process

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We wish to report a new living free-radical polymerization of exceptional effectiveness and versatility.[1] The living character is conferred by a readily available class of organic reagents (**1**) and is simple to perform. The


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2	Z=Ph, R=C(CH₃)₂Ph	**6**	Z=Ph, R=C(CH₃)₂CN
3	Z=Ph, R=CH(CH₃)Ph	**7**	Z=CH₃, R=CH₂Ph
4	Z=Ph, R=CH₂Ph	**8**	Z=Ph, R=C(CH₃)(CN)CH₂CH₂CH₂OH
5	Z=Ph, R=C(CH₃)(CN)CH₂CH₂CO₂Na	**9**	Z=Ph, R=C(CH₃)(CN)CH₂CH₂CO₂H

mechanism involves Reversible Addition−Fragmentation chain Transfer, and we have designated the process the RAFT polymerization. What distinguishes RAFT polymerization from all other methods of controlled/living free-radical polymerization is that it can be used with a wide range of monomers and reaction conditions and in each case it provides controlled molecular weight polymers with very narrow polydispersities (usually <1.2; sometimes <1.1).

Living polymerization processes offer many benefits. These include the ability to control molecular weight and polydispersity and to prepare block copolymers and other polymers of complex architecture−materials which are not readily synthesized using other methodologies. Therefore, one can understand the current drive to develop a truly effective process which would combine the virtues of living polymerization with versatility and convenience of free-radical polymerization.[2−4] However, existing processes described under the banner "living free-radical polymerization" suffer from a number of disadvantages. In particular, they may be applicable to only a limited range of monomers, require reagents that are expensive or difficult to remove, require special polymerization conditions (e.g. high reaction temperatures), and/or show sensitivity to acid or protic monomers. These factors have provided the impetus to search for new and better methods.

There are three principal mechanisms that have been put forward to achieve living free-radical polymerization.[2,5] The first is polymerization with reversible termination by coupling. Currently, the best example

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Scheme 1
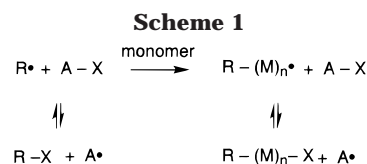
in this class is alkoxyamine-initiated or nitroxide-mediated polymerization as first described by Rizzardo et al.[6,7] and recently exploited by a number of groups in syntheses of narrow polydispersity polystyrene and related materials.[4,8]

The second mechanism is radical polymerization with reversible termination by ligand transfer to a metal complex (usually abbreviated as ATRP).[9,10] This method has been successfully applied to the polymerization of various acrylic and styrenic monomers.

The third mechanism for achieving living character is free-radical polymerization with reversible chain transfer (also termed degenerative chain transfer[2]). A simplified mechanism for this process is shown in
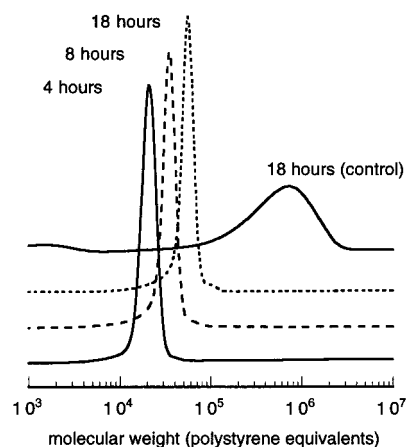

Figure 1. Molecular weight distributions for poly(styrene-*co*-acrylonitrile) polymerized by heating styrene and acrylonitrile (62:38 mole ratio) at 100 °C in the presence of cumyl dithiobenzoate (**2**) (0.0123 M) after 4 h ($\bar{M}_n = 20\,100$; $\bar{M}_w/\bar{M}_n = 1.04$), 8 h ($\bar{M}_n = 33\,000$; $\bar{M}_w/\bar{M}_n = 1.05$), and 18 h ($\bar{M}_n = 51\,400$; $\bar{M}_w/\bar{M}_n = 1.07$−the final time point corresponds to the last entry in Table 1). The molecular weight distribution for a similar polymerization performed without cumyl dithiobenzoate is also shown (control $\bar{M}_n = 424\,000$, $\bar{M}_w/\bar{M}_n = 1.70$).
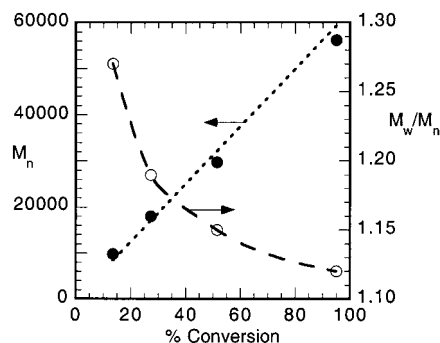

Figure 2. Evolution of molecular weight (polystyrene equivalents) and polydispersity with conversion during polymerization of MMA (7.01 M in benzene) performed at 60 °C in the presence of cumyl dithiobenzoate (**2**) (0.0111 M) and with AIBN (0.0061 M) as initiator (the final conversion point corresponds to the first entry of Table 1).

Table 1. Molecular Weight/Conversion Data for Polymers Formed by Polymerization of Various Monomers in the Presence of Dithio Compounds[a]

monomer(s)[b] ((concn (M) in solvent T°C))	dithio compound (concn (M) M × 10²)	initiator[c] (concn (M) M × 10²)	time (h)	$\bar{M}_n$[d]	$\bar{M}_w/\bar{M}_n$	convn[e] (%)
MMA (7.01 M benzene, 60)	**2** (1.11)	AIBN (0.61)	16	56200	1.12	95
MMA (7.48 M benzene, 60)	**2** (1.00)	Bz₂O₂ (0.40)	16	47100	1.04	78
MMA (7.01 M MEK, 60)	**2** (14.7)	AIBN (3.05)	24	6300	1.19	90
MMA (7.01 M benzene, 60)	**8** (1.13)	AIBN (0.61)	16	55300	1.05	92
BMA (emulsion, 80)[f]	**2** (f)	ACP (f)	2	57700	1.22	95
DMAEMA (2.54 M EtOAc, 60)	**9** (0.72)	ACP (0.17)	16	21500	1.13	62
BA (3.30 M MEK, 60)	**7** (3.40)	AIBMe (0.09)	2	6100	1.17	50
BA (2.79 M benzene, 60)	**4** (0.16)	AIBN (0.03)	8	92700	1.14	40
AA (2.92 M DMF, 60)	**3** (0.21)	AIBN (0.04)	4	13800	1.23	18
styrene (bulk, 110)	**2** (2.94)	thermal[g]	16	14400	1.04	55
styrene (bulk, 110)	**2** (0.49)	thermal[g]	16	88200	1.16	57
StySO₃Na (1.21 M H₂O, 70)	**5** (1.66)	ACP (0.42)	4	8000[h]	1.13	73
vinyl benzoate (bulk, 150)	**6** (3.49)	AB (0.02)	48	3500	1.29	12[i]
MMA/HEMA[j] (4.62 M EtOAc, 60)	**2** (1.11)	AIBN (0.61)	16	28000	1.21	75[i]
Styrene/AN[k] (bulk, 100)	**2** (1.23)	thermal[g]	18	51400	1.07	71

[a] Reaction mixtures were prepared to give the concentrations shown, degassed through three freeze−thaw−evacuate cycles, sealed under vacuum, and heated in a constant-temperature bath for the stated time. [b] Abbreviations (monomers): AA, acrylic acid; AN, acrylonitrile; BA, butyl acrylate; BMA, butyl methacrylate; HEMA, hydroxyethyl methacylate; DMAEMA, dimethylaminoethyl methacrylate; MMA, methyl methacrylate; StySO₃Na, *p*-styrenesulfonic acid sodium salt. Abbreviations (solvents): DMF, *N,N*-dimethylformamide; EtOAc, ethyl acetate; MEK, butan-2-one. [c] Abbreviations: AIBMe, 2,2′-azobis(methyl isobutyrate); AIBN, 2,2′-azobis(2-cyanopropane); ACP, 4,4′-azobis(4-cyanopentanoic acid); AB, 2,2′-azobis(2-methylpropane); Bz₂O₂, dibenzoyl peroxide. [d] Molecular weight data were obtained by gel permeation chromatography (GPC) with 10⁶, 10⁵, 10⁴, 10³, 500, and 100 Å Waters Ultrastyragel columns connected in series. Tetrahydrofuran (1.0 mL/min) was used as eluent. The GPC was calibrated with narrow polydispersity polystyrene standards. Samples for GPC were isolated by evaporation of monomer and solvent (no fractionation or precipitation was performed). The system was calibrated with narrow polydispersity polystyrene standards, and molecular weights are reported as polystyrene equivalents. [e] Conversions were determined gravimetrically following evaporation of monomer and solvent. Conversions were those obtained for the time indicated and are not a limiting conversion. [f] Emulsion polymerization procedure: A solution of ACP (71 mg) and **2** (17 mg) in BMA (1.7 g) was added to a stirred, degassed solution of sodium dodecyl sulfate (55 mg) in water (52 g) at 80 °C. Further **2** (71 mg) in BMA (2.7 g) was added over 10 min. BMA (16 g) was then added by syringe pump at 0.25 mL/min over 62 min. [g] No added initiator. [h] Molecular weight data were obtained by GPC with Waters Ultrahydrogel 500, 250, and 120 Å columns and with 0.1 M sodium nitrate/acetontrile (80:20) as eluent (0.8 mL/min). The system was calibrated with low polydispersity poly(*p*-styrenesulfonic acid sodium salt) standards. [i] Conversion determined by integration of the ¹H NMR spectrum. [j] Mole ratio of monomers 91:9. [k] Mole ratio of monomers: 62:38 (azeotropic composition).

Scheme 1.[5] The species A−X is a transfer agent which reacts with initiating (R•) or propagating radicals (R−(M)ₙ•) to give another transfer agent (R−X, R−(M)ₙ−X) and a species capable of initiating polymerization (A•).

A few living free-radical polymerization processes based on a reversible chain transfer mechanism have been described previously.[11−14] In these laboratories, we[13,14] examined polymerizations in the presence of methacrylate macromonomers where reversible chain transfer occurs by an addition−fragmentation sequence.[15] Gaynor et al.[11] have studied polymerization in the presence of certain alkyl iodides which give reversible chain transfer by homolytic substitution. Although these processes have been successfully used in the synthesis of block polymers and the polymerizations showed living characteristics under some conditions, neither process was capable of yielding polymers of very narrow polydispersity (<1.4) in batch polymerization. This limitation can be attributed to the relatively low chain transfer constant of the reagent used (ca. 0.3 in the case of methacrylate macromonomers in MMA polymerization[16]) and the consequent slow equilibration between active and dormant chains.

The RAFT process involves free radical polymerization in the presence of reagents **1** as exemplified by the dithioesters (**2**−**9**).[1] Examples of polymerizations performed with these compounds are provided in Table 1. The experimental conditions employed are those used for conventional free-radical polymerization. Polymerizations can be carried out in bulk, solution, emulsion or suspension. The usual azo or peroxy initiators are employed. There appear to be no particular limitations on solvent or reaction temperature. A wide range of molecular weights is possible (see Table 1).

Scheme 2[a]
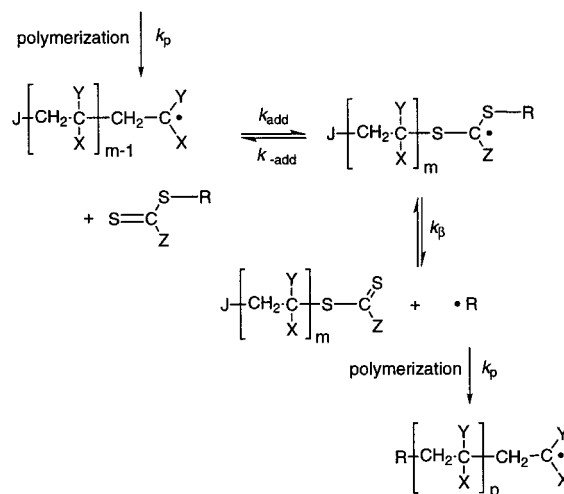
[a] J and R are species that can initiate free-radical polymerization, where they may be polymer chains (i.e. −[CH₂CXY]ₙ−) or they may be derived from radicals formed from the dithiocompound (**1**) or the initiator.

The living character of the RAFT process is indicated by (a) the narrow polydispersity product (see Table 1 and Figures 1 and 2), (b) a linear molecular weight−conversion profile (see, for example, Figure 2), (c) the predictability of the molecular weight from the ratio of monomer consumed to transfer agent (see Figure 2),[17] and (d) the ability to produce blocks or higher molecular weight polymers by further monomer addition.[1]

A major advantage of the RAFT polymerization process over other processes for living/controlled free-
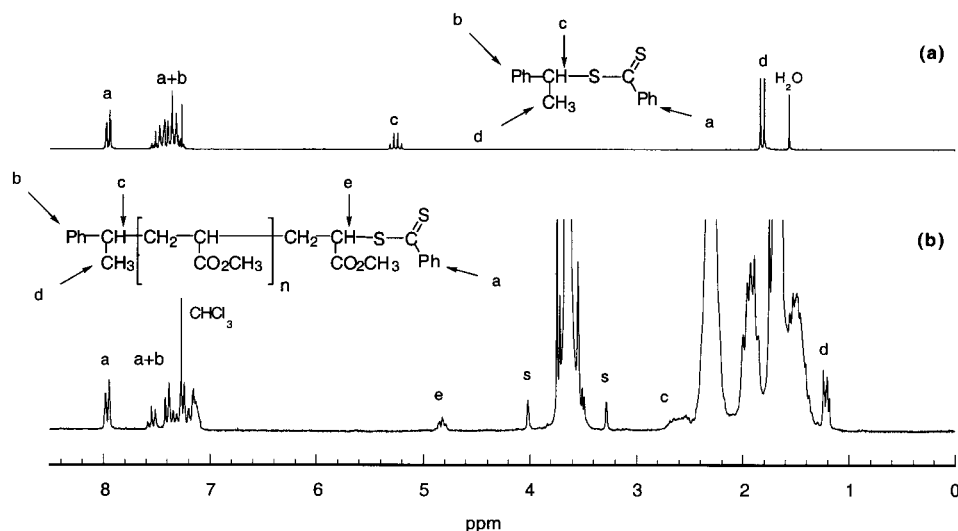
Figure 3. ^{1}H NMR spectrum (200.13 MHz, CDCl$_3$) of (a) 1-phenylethyl dithiobenzoate (**3**) and (b) poly(methyl acrylate) $\bar{M}_n$ 4700 (polystyrene equivalents), $\bar{M}_w/\bar{M}_n$ 1.05] prepared by polymerization of methyl acrylate (4.33 M in benzene) at 60 °C for 8 h in the presence of 1-phenylethyl dithiobenzoate (**3**) (0.0093 M) and with AIBN (0.00077 M) as initiator. The signals designated "s" are due to sidebands.

radical polymerization is that it is compatible with a very wide range of monomers including functional monomers containing, for example, acid (e.g. acrylic acid), acid salt (e.g. styrenesulfonic acid sodium salt), hydroxy (e.g. hydryoxyethyl methacrylate) or tertiary amino (e.g. dimethylaminoethyl methacrylate) groups (see Table 1). The process is similarly tolerant of functionality in the dithio-compound (e.g. compounds **5**, **8**, and **9**) and the initiator. This provides the ability to synthesize a wide range of narrow polydispersity polymers containing end or side chain functionality in a one-step process without any need for protection or deprotection. This can be used to advantage in the synthesis of block polymers and other products of more complex architecture.[1]

The mechanism of RAFT polymerization involves a reversible addition-fragmentation sequence in which transfer of the S=C(Z)S– moiety between active and dormant chains serves to maintain the living character of the polymerization (see Scheme 2). Evidence for this mechanism is provided by ^{1}H NMR (see, for example, Figure 3) and UV/visible spectra[18] which demonstrate that the S=C(Z)S– end group is retained in the polymeric product.

The effectiveness of reagents **1** in providing living character is attributed to their very high transfer constants which ensure a rapid rate of exchange between dormant and living chains. In fact, the transfer constants are too high to be measured using conventional techniques (e.g. the Mayo method). However, it is possible to show with the aid of kinetic modeling experiments that the effective transfer constant[19] must be greater than 100 in order to obtain a polymer with a polydispersity of 1.1 at low conversions.[5]

The choice of Z and R in reagents **1** is crucial to the success of the RAFT process. To ensure a high transfer constant, Z should activate (or at least not deactivate) the C=S double bond toward radical addition. Suitable Z groups are aryl and alkyl (see Table 1, for examples). On the other hand, compounds where Z is dialkylamino or alkoxy (ie. dithiocarbamates and xanthates respectively) have low transfer constants and are relatively ineffective.[20] Thus, the RAFT process is quite distinct in terms of the chemistry involved from the photoin-

iferter process first described by Otsu et al.[21,22] The R group should be a good free–radical leaving group (e.g, cumyl, cyanoisopropyl), and as an expelled radical, R$^•$ should be effective in reinitiating free-radical polymerization.

Further details of this novel form of living radical polymerization will be presented in future publications.

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(17) The expected molecular weight can be calculated from the expression: $([M]_i/[\mathbf{1}]_i)CM_0$ where $[M]_i$ and $[\mathbf{1}]_i$ are the initial concentrations of monomer and the dithio compound respectively, C is the fractional conversion, and M_0 is the molecular weight of the monomer. The agreement between found and calculated molecular weight is within experimental error ($\pm10\%$).

(18) The polymers made in the presence of reagents **1** are colored due to the presence of the thiocarbonylthio chromophore. Colors range from pale yellow through pink depending on the substituents Z and R. This chromophore is an aid in characterization. The chromophore can be readily removed, and the polymer decolorised, by reacting the thiocarbonylthio group with various reagents including amines [to produce a thioamide and a thiol-terminated polymer (Haraoubia, R.; Bonnans, C.; Gressier, J.-C.; Levesque, G. *Makromol. Chem.* **1982**, *183*, 2383)] or sodium hypochlorite or hydroperoxide solution [to provide a sulfine (Carreta, F.; Le Nocher, A.-M.; Leriverend, C.; Metzner, P.; Pham, T. N. *Bull. Soc. Chim. Fr.* **1995**, *132*, 67)]. For leading references on the reactions of dithio compounds, see: Kato, S.; Ishida, M. *Sulfur Rep.* **1988**, *8*, 155. Mayer, R.; Scheithauer, S. In *Houben–Weyl Methods of Organic Chemistry*; Buechel, K. H., Falbe, J., Hagemann, H., Hanack, M., Eds.; Thieme: Stuttgart, Germany, 1985; Vol. E, p 891.

(19) The rate constant for chain transfer by addition-fragmentation is defined as follows: $k_{tr} = k_{add} \, k_\beta/(k_{-add} + k_\beta)$; see Scheme 2 for definition of terms.

(20) These compounds have very low transfer constants, typically <0.1. For example, the transfer constant of *S*-benzyl *N,N*-diethyldithiocarbamate in styrene polymerization has been measured as 0.009 at 80 °C while that of *S*-(2-cyanoprop-2-yl) *O*-ethylxanthate in MMA polymerization at 60 °C is 0.08 (Krstina, J.; Le, N.; Moad, C. Unpublished results).

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