Radical Copolymerization of Maleimide with Ethyl α-Ethylacrylate and α-Ethylacrylic Acid via RAFT

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ABSTRACT: The copolymerization of maleimide (MI) with α-ethylacrylic acid (EAA) and with ethyl α-ethylacrylate (EEA) in the presence of 2-phenylprop-2-yl dithiobenzoate (PPDB) was investigated. The copolymerization of MI and EAA was difficult to conduct with the reversible addition–fragmentation chain transfer (RAFT) mechanism because reinitiation of expelled radicals by fragmentation chain transfer was inhibited by the association of EAA in polar solvent and the strong interaction of the imino of MI with the carboxyl of EAA between the propagation chains. When the carboxylic group of EAA was esterified, then the copolymerization went well via RAFT, and alternating copolymers with controlled molecular weight were obtained. Combining by electron spin resonance showed a different result. It was found that before 30% of the comonomer conversion had occurred, the copolymer poly(EEA-co-MI) showed increasing molecular weight with the conversion and a rather narrow molecular weight distribution; then the molecular weight of the copolymer began to retard. This phenomenon of retardation was aggravated at high temperature. © 2004 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 42: 3828 –3835, 2004

Keywords: radical addition-fragmentation chain transfer; copolymerization; maleimide; α-ethylacrylic acid; ethyl α-ethylacrylate; charge transfer; molecular weight distribution

INTRODUCTION

Currently, polymers with well-defined architecture and controlled composition are of considerable interest for their academic and industrial uses.1–3 Now some important results have been achieved in controlled radical polymerization, and atom transfer radical polymerization,4 nitroxide-mediated stable radical polymerization,5 and reversible addition–fragmentation chain transfer (RAFT),6,7 which are widely used for synthesis of a variety of polymers with different structures and compositions.

α-Substituted acrylates or acids are very important and interesting monomers; the corresponding polymers are widely used and not only as superabsorbents, scale inhibitors, and dispersants8; some of them also have shown physiological reactivity in the human body.9,10 It was found, however, that α-alkylacrylic esters and acids, except methacrylic ester and acid, were reluctant to polymerize because of the steric hindrance of the α-substituent.11 Maleimide (MI) and its derivatives are also a kind of very useful monomer. Their homopolymers or copolymers can be used as heat-resistant materials.12 Fields13 found that a low-molecular-weight copolymer with 14%–25% succinimide rings in the main chain showed biological activity for several transplantable tumors.

Recently, we found that MI could be copolymerized with a series of α-substituted acrylates and
acrylic acids via a charge-transfer complex (CTC) mechanism. Some of these, for example, the copolymer of MI with α-ethylacrylic acid (EAA) showed low toxicity and high activity for suppressing metastases of carcinoma. However, the synthesis of this kind of copolymer is mainly carried out by common radical polymerization, so the molecular weight of copolymers is uncontrollable and distribution is wide.

To prepare this kind of pharmaceutical copolymer with controlled molecular weight and narrow distribution, we tried using the RAFT method.

This contribution describes the copolymerization of MI with EAA and with ethyl α-ethylacrylate (EEA) via RAFT. Some special phenomena in the copolymerization also are discussed.

EXPERIMENTAL

Materials

Azobisisobutyronitrile (AIBN) was recrystallized from methanol. Dioxane was treated with fresh sodium and distilled. All other reagents were purified by standard methods.

Monomer Preparation

MI was prepared as described in the literature with a yield of 43% and an mp of 89–90 °C. EAA and EEA also were prepared as reported previously with yields of 21% and 29%, respectively. Purification was carried out by distillation under reduced pressure; EAA was collected with fractionation at 64–65 °C and 15 mmHg for EEA was collected.

Preparation of Chain Transfer Agents

2-Phenylprop-2-yl dithiobenzoate (PPDB) was prepared according to the published procedure with a yield of 32%. The product was an oily liquid dark purple in color [NMR (CDCl₃, ppm): 2.05 (s, 6H), 7.20–7.60 (m, 8H), 8.06 (m, 2H)].

Copolymerization

Accurately weighed MI, EEA or EAA, AIBN, PPDB, and a given amount of dioxane (initial concentration of comonomer MI and EEA or MI and EAA: 5.0 mol/L) were added to a 100-mL glass ampoule, degassed three times by freeze-pump-thaw cycles at 77 K, and sealed under N₂. Copolymerization in different monomer feed ratios was performed at 70 ± 1 °C or 90 ± 1 °C. After a given time, the ampoules were removed from the oil bath and dipped in liquid nitrogen to stop the copolymerization. The copolymer was purified twice by a procedure of dissolution/precipitation with dioxane/ether and extracted with ether for 24 h.

Measurements

¹H NMR spectra were recorded on a Bruker DMX-500 nuclear magnetic resonance (NMR) instrument with tetramethylsilane (TMS) as internal standard and CDCl₃ as solvent. IR spectra were scanned by a Magna-550 FTIR spectrometer. Elemental analysis was determined by a Carlo Erba 1106 elemental analyzer. Electron spin resonance (ESR) measurements were performed by placing degassed sealed tubes containing refined comonomers, AIBN initiator, RAFT agent, and benzene in the preheated cavity of the ESR spectrometer at 80 °C, using an ER 200D-SRC Bruker ESR spectrometer operating at X-band (9.67 GHz) with a TE mode cavity. Molecular weight and molecular weight distribution were derived with a Agilent1100 gel permeation chromatographer (GPC) with refractive index detector and UV–vis detector (wavelength 190–950 nm), two Mix-C PL-gel columns (500 Å, relative molecular weight 500–3 × 10⁶), with an injection volume of 20 µL, THF (or DMF) as the solvent and eluent, and a flow rate of 0.2–5 mL/min. GPC was calibrated with monodispersed polystyrene standards.

RESULTS AND DISCUSSION

Copolymerization of MI with EAA via RAFT

As we mentioned before, MI and EAA could constitute the charge transfer complex, so their common radical copolymerization was investigated. The copolymerized product formed via RAFT was a pale-pink powder soluble in dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and dioxane. The MI and EAA, however, were very difficult to homopolymerize in the same conditions, as it was easy to separate them.

The IR spectra of the poly(MI-co-EAA) showed the characteristic bands of MI and EAA. The peaks at 2977 cm⁻¹ (—CH₂—) and 1712 cm⁻¹
(C=O) were attributed to the EAA component, and those at 1774 cm\(^{-1}\) (C=O) to the MI component. The \(^1\)H NMR spectrum of the copolymer shown in Figure 1 indicates the proton signals of the \(-\text{COOH}\) group of EAA at 12.6 ppm and the \(-\text{NH}\)—group of MI at 11.1 ppm.

The copolymer of MI and EAA was obtained. However, as the experimental data listed in Table 1 show, no matter how the experimental conditions were changed, the polydispersity index remained broad, with most values larger than 2.0. Furthermore, the molecular weight (\(M_n\)) values obtained from GPC were generally larger than the theoretical ones, though the conversions of comonomers were still low. Thus, it was concluded that copolymerization of MI with EAA via RAFT was uncontrolled in our experiment conditions. We think that there are two causes for this phenomenon. (1) In dioxane EAA could be associated by itself and with solvent\(^{19}\) (Scheme 1). When MI and EEA are copolymerized, the propagating chain should react with the comonomers that are composed of MI with aggregates of EAA and not react with a single EAA molecule. So the theoretical value of the molecular weight of copolymer, which was derived from the comonomer

![Figure 1. \(^1\)H NMR spectrum of poly(MI-co-EAA).](image)

**Table 1.** Copolymerization of MI with EAA in the Presence of PPDB**

<table>
<thead>
<tr>
<th>No.</th>
<th>[PPDB] (Initiator)</th>
<th>Time (h)</th>
<th>(M_n) (theory)*</th>
<th>(M_n) (exptl)</th>
<th>(M_n/M_n)</th>
<th>Solvent</th>
<th>Conv* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2:1</td>
<td>30.0</td>
<td>(1.0 \times 10^4)</td>
<td>(6.3 \times 10^4)</td>
<td>2.96</td>
<td>Dioxane</td>
<td>2.20</td>
</tr>
<tr>
<td>2</td>
<td>2:1</td>
<td>63.5</td>
<td>(7.2 \times 10^4)</td>
<td>(1.7 \times 10^5)</td>
<td>2.66</td>
<td>Dioxane</td>
<td>15.9</td>
</tr>
<tr>
<td>3</td>
<td>3:1</td>
<td>30.0</td>
<td>(2.3 \times 10^4)</td>
<td>(8.7 \times 10^4)</td>
<td>2.63</td>
<td>Dioxane</td>
<td>5.07</td>
</tr>
<tr>
<td>4</td>
<td>3:1</td>
<td>63.5</td>
<td>(2.4 \times 10^4)</td>
<td>(2.3 \times 10^5)</td>
<td>2.31</td>
<td>Dioxane</td>
<td>5.21</td>
</tr>
<tr>
<td>5</td>
<td>3:1</td>
<td>45.3</td>
<td>(1.6 \times 10^4)</td>
<td>(1.2 \times 10^4)</td>
<td>1.93</td>
<td>DMF</td>
<td>3.47</td>
</tr>
<tr>
<td>6</td>
<td>No PPDB</td>
<td>12.0</td>
<td>(3.0 \times 10^5)</td>
<td>(4.31)</td>
<td></td>
<td>Dioxane</td>
<td>24.3</td>
</tr>
</tbody>
</table>

* Conv: Conversion; **[MI]:[EAA] = 1:1, \([M]\_\text{EAA}_0 + [M]\_\text{MI}_0 = 5.0\ \text{mol/L};\) dioxane volume: 2.5 mL; temp: 70 °C.

*Theoretical \(M_n = ([M]\_\text{MI}_0 + [S]\_\text{MI}_0) \times \text{Conversion} \times ([97.07 + 128.17]/2 \times [\text{AIBN}]_0 + [\text{PPDB}]_0).\) Here \([M]\_\text{MI}_0, [S]\_\text{MI}_0, [\text{AIBN}]_0,\) and \([\text{PPDB}]_0\) are the initial total monomer, solvent, AIBN, and PPDB concentration, respectively; 97.07 and 128.17 are the molecular weights of MI and EEA, respectively.
pair composed of one MI with one EAA, should be lower than that of the copolymer obtained from the comonomer pair composed of one MI with \( n \) EAA (\( n \) is the degree of association of EAA). (2) In the RAFT process there is a reinitiation process, and the copolymerization rate is dependent on the activity of the expelled radical formed by transfer of the chain fragment. In our previous investigation\(^{20} \) it was found that the aggregation of EAAs in dioxane and their interaction with MI exerted a great effect on the copolymerization of MI with EAA. So the interaction of the imino of MI with the carbonyl of EAA in the same or different copolymer chains shown in Scheme 2 also interfered with the fragmentation and transfer of radical chains, leading to the uncontrollability of this copolymerization system.

**Copolymerization of MI with EEA via RAFT**

To resolve the problem of the uncontrollability of the copolymerization of MI with EAA via RAFT, the carboxyl group of EAA was esterified, and EEA was prepared. The copolymerization of MI with EEA was then conducted under the same conditions as with the system of MI and EAA. The copolymerized product also was soluble in DMF, DMSO, THF, and dioxane, and no homopolymer was detected.

The IR spectra of the poly(MI-co-EEA) showed the characteristic bands of MI and EEA. The peaks at 2981 cm\(^{-1} \) (\(-\text{CH}_2\)) and 1719 cm\(^{-1} \) (C=O) were attributed to the EEA component, and that at 1777 cm\(^{-1} \) (C=O) to the MI component. The \(^1\)H NMR spectrum of the copolymer shown in Figure 2 indicates the proton signals of the \(-\text{COOCH}_2\) group of EAA at 3.9 ppm and the \(-\text{NH}-\) group of MI at 11.2 ppm. At 7.0–8.0 ppm, the proton signals of the phenyl group of PPDB also were presented.

Table 2 shows the molecular weights \((M_n)\) and polydispersities \((M_w/M_n\) vs conversion). The data indicate that the molecular weight of the copolymers increased linearly with conversion, and the experimental values were close to the theoretical ones, assuming quantitative initiation. In all cases the molecular weight distribution was less than 1.5. These data show that copolymerization of MI with EEA was controlled via RAFT, and it was also confirmed that the uncontrollability of copolymerization of MI and EAA by RAFT could be attributed to the association of EAA and the interaction of the imino of MI with the carboxyl of EAA between the propagation chains. To further expound the kinetic behavior of this copolymerization system, copolymerization rates at different temperature were investigated. Figure 3 shows the semilogarithmic curves of conversion with time. It shows that when the conversion was lower than approximately 30%, the rates of copolymerization increased linearly with time. However, when the conversion approached 30%, the
polymerization seemed to be retarded. At 90 °C the phenomenon of retardation was aggravated, and the rate appeared to have a sharper retardation than that did at 70 °C.

There are different explanations for the retardation of polymerization using the RAFT agent Monterio et al.\textsuperscript{21} postulated, with a combination of simulations and experimental evidence, that a cross-termination mechanism (Scheme 3) explained this phenomenon. However, Stenzel et al.\textsuperscript{22} showed that when using dioxane or THF as solvents in the RAFT system, the peroxide impurities might react easily with the RAFT agent, leading to oxidation of the dithioester and a loss of radicals. Vana et al.\textsuperscript{23} confirmed the oxidation of end groups of RAFT agents by electrospray ionization mass spectrometry. In our system the copolymerization was performed at a temperature 70 °C or higher, conditions that went against the Monterio approach (who used a lower temperature). To have a deep understanding of the copolymerization of MI and EEA via RAFT, ESR also was used to monitor the whole process. Figure 4(a) shows the ESR spectrum acquired by integrating the signal of this system from the reacting 12 min to 19 min. The signal was well resolved and clearly distinct from other species that could be present in the system. Compared with the g-

![Image](https://example.com/image.png)

**Figure 2.** $^1$H NMR spectrum of poly(MI-co-EEA).

### Table 2. Copolymerization of MI with EEA in the Presence of PPDB*

<table>
<thead>
<tr>
<th>No</th>
<th>[PPDB] (Initiator)</th>
<th>Conversion (%)</th>
<th>$M_n$ (theory)</th>
<th>$M_n$ (exptl)</th>
<th>$M_w/M_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1</td>
<td>15</td>
<td>$1.1 \times 10^3$</td>
<td>$1.5 \times 10^3$</td>
<td>1.10</td>
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<tr>
<td>2</td>
<td>2.1</td>
<td>19</td>
<td>$1.9 \times 10^3$</td>
<td>$2.3 \times 10^3$</td>
<td>1.15</td>
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<tr>
<td>3</td>
<td>2.1</td>
<td>26</td>
<td>$2.7 \times 10^3$</td>
<td>$3.1 \times 10^3$</td>
<td>1.23</td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
<td>31</td>
<td>$3.1 \times 10^3$</td>
<td>$3.6 \times 10^3$</td>
<td>1.30</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>37</td>
<td>$3.5 \times 10^3$</td>
<td>$3.9 \times 10^3$</td>
<td>1.35</td>
</tr>
<tr>
<td>6</td>
<td>2.1</td>
<td>45</td>
<td>$4.2 \times 10^3$</td>
<td>$4.4 \times 10^3$</td>
<td>1.40</td>
</tr>
</tbody>
</table>

* [MI]:[EAA] = 1:1, [M$_{EAA}$]$_0$ + [M$_{MI}$]$_0$ = 5.0 mol/L; dioxane volume: 2.5 mL; temp: 70 °C.
factor value reported in the literature \((g = 2.0043)\) for the intermediate radical when PPDB was used,\(^2\) the \(g\)-factor value in our system was 2.0040, similar to the reported value. The experimental data confirmed that in our system the reactive intermediate radicals were really produced by PPDB. Throughout the whole process of RAFT, ESR signals were picked up at 1-min intervals. At the beginning, no obvious difference was observed in the spectra picked up in the different times, as Figure 4(b,c) shows, until the conversion was more than 30%. Figure 4(d) is the signal of 129 min. At this time the comonomer conversion was more than 30%, and its intensity decreased. The ESR measurement supplied strong evidence for the kinetic behavior of copolymerization, that is, the variation of the concentration of the intermediate radical was a slow and cumulative process, and when the conversation was less than 30%, copolymerization could be conduct because there were still some dithioesters that remained, although some of them were oxidized. When the conversion was more than 30%, the radical concentration of the RAFT agent was so low that the copolymerization was retarded. The longer the time and the higher the temperature, the easier was the oxidation of the RAFT agent. Therefore, in our system a loss of activity was mainly attributed to the oxidation of the RAFT agent.

Copolymer Microstructure

The copolymer compositions in the different feed ratios, determined by elemental analysis, are listed in Table 3. The reactivity ratios \(r_1\) and \(r_2\) for the monomers MI and EEA, respectively, were evaluated by the Kelen–Tüdos\(^2\) and Fineman–Ross methods.\(^2\) At low conversions the values were \(r_1 = 0.08 \pm 0.01\) and \(r_2 = 0.41 \pm 0.04\) for the former and \(r_1 = 0.05 \pm 0.02\) and \(r_2 = 0.35 \pm 0.03\) for the latter. The product of \(r_1r_2\) was in the range of 0.02–0.03, which is less than 1. This means that the copolymerization of MI and EEA should be carried out with an alternating mechanism. As shown in Table 3, though the feed ratio varied from 4:6 to 8:2 for MI/EEA, the copolymer composition was near 50:50. The statistical distribution of the monomer sequences, and the contents of MI–MI, EEA–EEA, and MI–EEA in the copolymer chains were calculated using the following equations\(^2\):

\[
X = \phi_1 - 2\phi_1(1 - \phi_1)/(1 + [(2\phi_1 - 1)^2 + 4r_1 \cdot r_2\phi_1(1 - \phi_1)^{1/2}])
\]

\[
Y = (1 - \phi_1) - 2\phi_1(1 - \phi_1)/(1 + [(2\phi_1 - 1)^2 + 4r_1 \cdot r_2\phi_1(1 - \phi_1)^{1/2}])
\]

\[
Z = 4\phi_1(1 - \phi_1)/(1 + [(2\phi_1 - 1)^2 + 4r_1 \cdot r_2\phi_1(1 - \phi_1)^{1/2}])
\]

where \(r_1\) and \(r_2\) are the reactivity ratios of MI and EEA, respectively; \(\phi_1\) is the molar fraction of MI in the copolymer; and \(X, Y,\) and \(Z\) are the mole fractions in the copolymer of the MI–MI, EEA–EEA, and MI–EEA sequences, respectively. Using this method, we found that the content of the MI–EEA alternating sequence in copolymer was as high as almost 80%, which confirms that poly(MI-co-EEA) is an alternating copolymer.

**CONCLUSIONS**

Copolymerization of MI with EAA and of MI with EEA was investigated. The copolymerization of MI with EEA cannot be conducted well via RAFT
because of the association of EAA in polar solvent and the strong interaction of the imino of MI with the carboxyl of EAA between the same and different propagation chains. When the carboxylic group was esterified, then the copolymerization of MI with esterified EAA (EEA) went well via RAFT, and the alternating copolymer of MI with EEA was obtained. It was found that before 30% of the comonomer conversion, the molecular weight of the copolymer increased with the conversion and the molecular weight distribution was rather narrow; then the molecular weight of the copolymer began to retard. The phenomenon of retardation was aggravated at high temperature. This result is consistent with a loss of radicals during the course of the copolymerization, which was confirmed by ESR. It may be attributed to the oxidation of the RAFT agent by peroxide impurities in dioxane.

We appreciate the support from the Natural Science Foundation of China (No. 30070882).

**Table 3.** Effect of Feed Ratio on Copolymerization of MI (M₁) with EEA (M₂)

<table>
<thead>
<tr>
<th>Run</th>
<th>MI in feed (F₁) (mol %)</th>
<th>Conv. (%)</th>
<th>N (%)b</th>
<th>MI (mol %)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>2.05</td>
<td>4.98</td>
<td>41.0</td>
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<tr>
<td>2</td>
<td>50</td>
<td>3.45</td>
<td>5.26</td>
<td>43.1</td>
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<td>3</td>
<td>60</td>
<td>2.78</td>
<td>5.62</td>
<td>45.7</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>2.49</td>
<td>6.25</td>
<td>50.2</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>6.25</td>
<td>6.94</td>
<td>55.0</td>
</tr>
</tbody>
</table>

* [M₁]₀ + [M₂]₀ = 8.0 mol/L; [AIBN]₀ = 3.0 × 10⁻² mol/L; [PPDB]₀ = 9 × 10⁻² mol/L; dioxane volume: 15 mL; temp: 70 °C.

b Average nitrogen content in the copolymer was obtained by duplicate analysis.

c MI (mol %) in copolymer was calculated as F₁,

\[
F₁ = \frac{1}{\frac{N}{97.07} - 1} \times 100\% \quad \text{where } N \text{ is the nitrogen content (mol %) in copolymer and 97.07 and 128.17 are the molecular weight of MI and EEA, respectively.}
\]

**REFERENCES AND NOTES**
