Studies on the Free Radical Polymerization of *N*-Vinylpyrrolidinone in 3-Methylbutan-2-one

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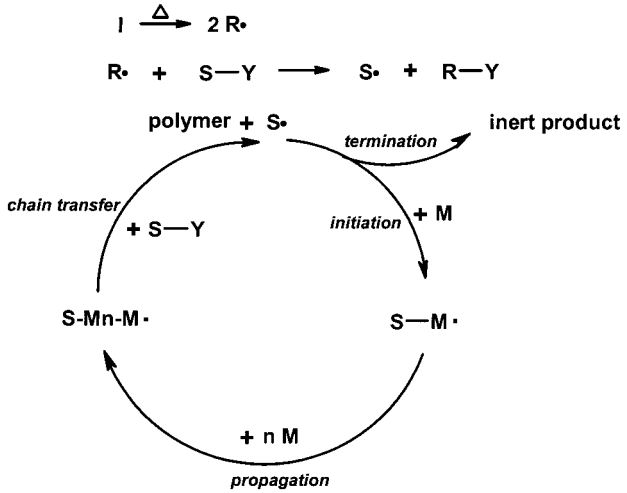
ABSTRACT: *N*-vinylpyrrolidinone was polymerized in 3-methylbutan-2-one, which acted as both solvent and transfer agent. The main products of this reaction were poly(*N*-vinylpyrrolidinone)s with methyl ketone chain ends. These polymers were formed by transfer to solvent involving abstraction of hydrogen at either the isopropyl or 1-methyl position. MALDI−TOF mass spectrometry was used to fully characterize the polymers, and several other initiation and termination events were found to occur. Thus end groups associated with initiation by and combination with the primary radical were observed. Isopropyl end groups were formed as a result of fragmentation of 3-methylbutan-2-on-1-yl radical produced as a consequence of transfer to the 1-methyl group of 3-methylbutan-2-one. This fragmentation also yielded ketene, which underwent initial propagation followed by rapid extraction of a hydrogen atom from 3-methylbutan-2-one and yields aldehyde end groups that were observed in both NMR and MALDI−TOF spectra. Also, end groups associated with termination by combination between propagating and solvent radicals were observed.

Introduction

Utilization of transfer reactions in free radical polymerizations is an important route to chain-end functional oligomers and is illustrated in Scheme 1.[1] The polymerizations are carried out in the presence of compounds that possess liable atoms or groups, which are abstracted in radical transfer reactions. Ideally, initiations by initiator primary radicals are negligible. Also, the radicals derived from the transfer step should be reactive enough to reinitiate the kinetic chain and bimolecular terminations should be minimized. However, the polymerizations are often complicated by other concurrent reactions that lead to the formation of products with end groups of undesired functionalities.

Poly(*N*-vinylpyrrolidinone) (PNVP) possesses good biocompatibility, and devices based on hydrogels of this material have found several medical applications. The propagating PNVP radical is highly reactive, and it is prone to transfer. Thus radical polymerizations of *N*-vinylpyrrolidinone (NVP) in some organic solvents (e.g., toluene and alcohols) are subject to significant chain transfer to solvent.[2] These observations have been used by Sanner et al. to synthesize oligoNVP with hydroxyl functionality by carrying out polymerizations in 2-propanol using cumene hydroperoxide as an initiator.[3] The incorporation of the 2-propanol fragments at the chain ends was proven by ^{1}H nuclear magnetic resonance (NMR) spectrometry that clearly revealed the methyl protons corresponding to the hydroxyisopropyl end groups. Their calculations based on the integrated ^{1}H NMR spectrum and the polymer molecular weight determined by vapor pressure osmometry gave an average value of 1.3 hydroxyisopropyl end groups per chain. This result implies that significant termination by bimolecular combination occurs, between either a primary solvent radical and the propagating chain or two propagating chains. However, functionalized oligoNVP could be readily synthesized by free radical polymerization using functional organic solvents.

Scheme 1. Simplified Mechanism of a Free Radical Chain Transfer Polymerization.



here I is initiator; R• is initiator primary raidcal; S is transfer agent fragment; Y is liable atom or group; and M is monomer

Ferruti and co-workers reported the application of this methodology for synthesising primary hydroxyl end-functionalized oligoNVP by using 2-isopropoxyethanol as a solvent.[4,5] More recently, transfer to esters has been used to prepare oligoNVP with lactone or ester end groups.[6]

During our work on ab initio cationic polymerization[7] and drug delivery,[8] it was desirable to synthesize oligoNVPs with methyl ketone end groups that could then be transformed into oligomers with sily enol ether end groups. These oligomers could be prepared by radical polymerization with chain transfer to the solvent, 3-methyl-2-butanone. In this article, we report a detailed study of these polymerizations by combined application of MALDI−TOF mass spectrometry and NMR spectrometry. Recently, MALDI−TOF mass spectrometry has been successfully used for end group

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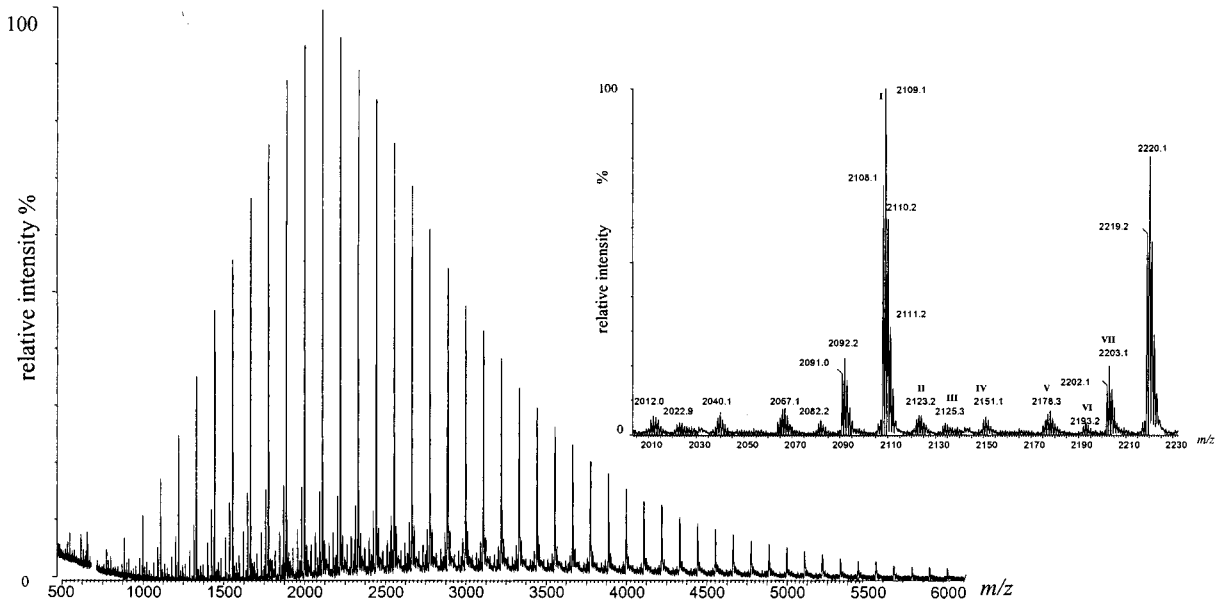


Figure 1. MALDI−TOF mass spectrum of AIBN-initiated oligoNVP molar ratio in feed: NVP:AIBN:MB = 100:0.34:643.

analysis,[1,9−16] evaluating chain termination modes[17] and for determining chain transfer coefficients in free radical polymerizations.[18]

Experimental Section

Materials. Azobisisobutyronitrile (AIBN) was purchased from Merck and other chemicals were from Aldrich. NVP was distilled prior to polymerization. AIBN and benzoyl peroxide (BPO) were recrystallized from methanol and chloroform/methanol (50/50, v/v), respectively. 3-Methylbutan-2-one (MB) and cumene hydroperoxide (CHP) were used as received without any further purification.

Polymerizations. All polymerizations were conducted in a two-necked round-bottom flask equipped with a magnetic stirrer, a nitrogen inlet and a water-cooling reflux condenser. Polymerization temperatures were maintained by using an oil bath with precision temperature control of ±1 °C. In a typical run, NVP (20.17 g, 181.48 mmol), AIBN (0.10 g, 0.61 mmol), and MB (100.57 g, 1.168 mol) were added to a 250 cm^3 flask and deaerated by bubbling with nitrogen at room temperature for 45 min. After this, the flask was immersed in an oil both at 70 °C to start the polymerization. Unless stated otherwise, polymerizations were performed at 70 °C for 24 h. Polymers were collected by removal of MB under reduced pressure, then purified by precipitation from dichloromethane with diethyl ether three times, and finally dried in vacuo at room temperature for 48 h. For NMR spectroscopy, the residual diethyl ether in the polymer samples was removed by distillation with chloroform or dichloromethane on a rotary evaporator.

MALDI−TOF MS. MALDI−TOF mass spectra were obtained with a Micromass TofSpec 2E mass spectrometer. The instrument was operated in positive ion reflectron mode with an accelerating potential of +20 kV. Spectra were acquired by averaging at least 100 laser shots. Dithranol was used as a matrix and chloroform as a solvent. Sodium iodide was dissolved in methanol and used as the ionizing agent. Samples were prepared by mixing 20 μL of polymer solution (6−8 mg cm^{-3}) with 20 μL of matrix solution (10 mg cm^{-3}) and 10 μL of a solution of ionizing agent (2 mg cm^{-3}). Then 1.0 cm^3 of these mixtures was deposited on a target plate and the solvent was removed in a stream of nitrogen. An external multipoint calibration was performed by using bradykinin (1060.2 g mol^{-1}), angiotensin (1296.5 g mol^{-1}), substance P (1347.6 g mol^{-1}), reuin substrate tetradecapeptide (1759.0 g mol^{-1}), and insulin (5733.5 g mol^{-1}) as standards.

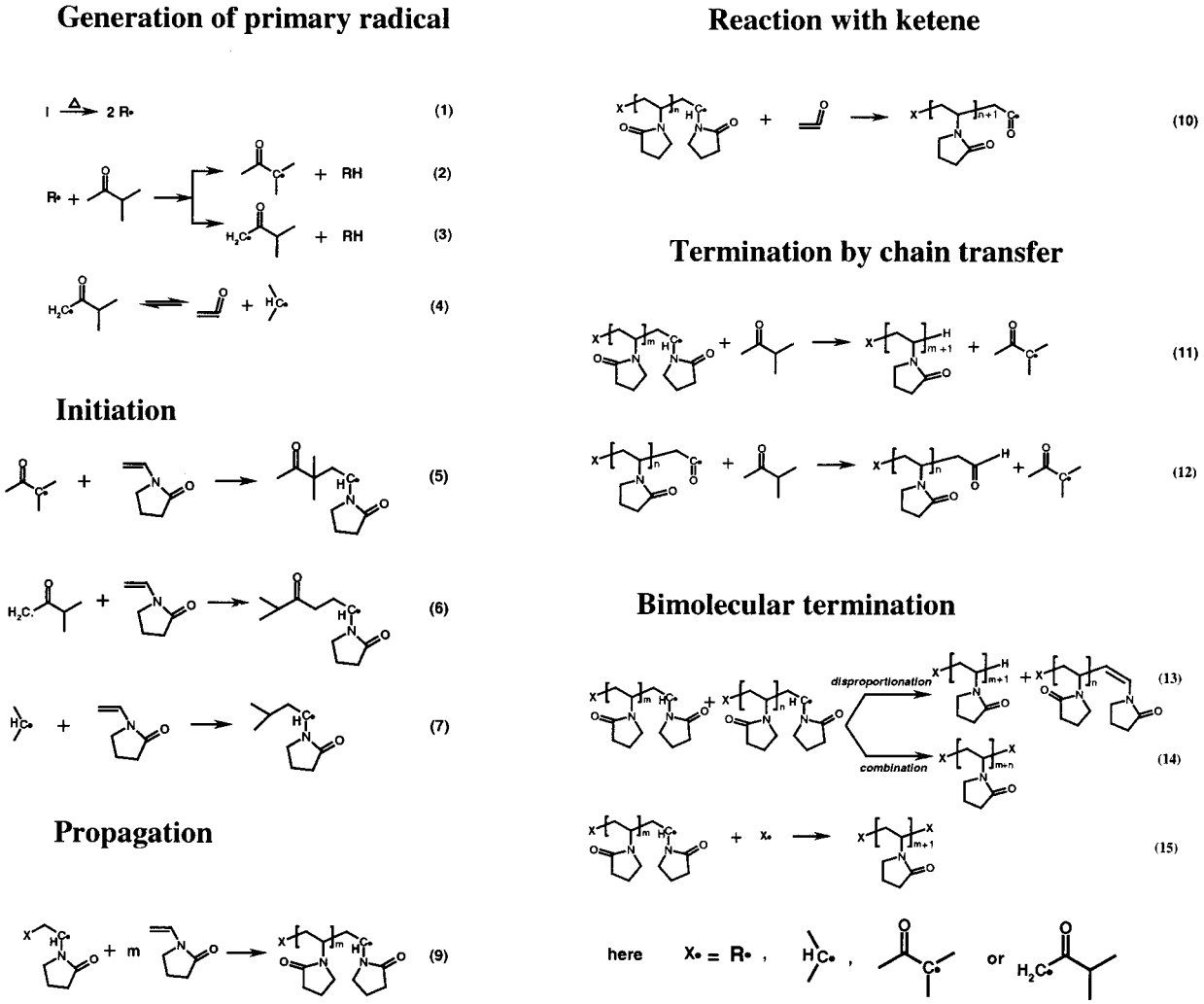
Nuclear Magnetic Resonance Spectroscopy. ^{1}H NMR spectra were recorded on a Varian NMR200 at 200 MHz. Samples were prepared at a concentration of about 1.0 wt % in $CDCl_3$. The spectra were referenced using tetramethylsilane (TMS) as an internal standard.

Results and Discussion

Figure 1 shows a typical MALDI−TOF mass spectrum of oligoNVP prepared using AIBN as an initiator. Macromolecular ion peaks were clearly detected in a range from around m/z 600 to 6000 with the most intensive peak at about m/z = 2109. Figure 1 also shows an expansion of the spectrum. Seven series of ion peaks separated by the corresponding m/z equal to the mass of the NVP repeat unit (monoiostopic mass = 111.07 g mol^{-1}) are clearly observable, and the peaks are isotopically resolved.

The synthesis of functional oligomers by transfer to added functional transfer agents or solvent relies on the transfer being the dominant termination reaction and initiation by the radical derived from transfer being the dominant initiation process. If these criteria are fully satisfied, assuming that the abstraction of the isopropyl hydrogen is the predominant transfer process (see reactions 2, 5, 9 and 11 in Scheme 2), then the major product from the polymerizations reported here would be oligoNVPs with α-3-methylbutan-2-on-3-yl, ω-H end functionality. In Figure 2, an isotopic pattern of the most abundant series of ion peaks (labeled as peak I in Figure 1) in the MALDI−TOF mass spectrum is compared with a simulation of the sodium ion adduct of an oligomer with the functionality proposed above and consisting of 18 NVP repeat units. The calculated mass accuracy is about 0.01% and the resolution is around 5021 ($m/\Delta m$, fwhm) at this m/z. The simulated and experimental spectra essentially match, but the first two isotopic peaks in the experimental spectrum (marked with ∗), although small, are absent from the simulation. The source of these peaks is discussed further below. The series of ion peaks I in Figure 2 can thus be assigned to the sodium ion adducts of oligoNVPs generated by initiation by the 3-methylbutan-2-on-3-yl radical and termination by chain transfer to MB. The high relative intensity of this series of ion peaks suggests that α-3-methylbutan-2-on-3-yl, ω-H are the dominant chain ends.

Scheme 2. Mechanistic Representation for the Radical Polymerization of NVP in MB.



The ratio of mass to charge number for a monoisotopic macromolecule is given by the following equation:[19]

$$\left(\frac{m}{z}\right)^{z+} = n\cdot\frac{m_{\mathrm{mon}}}{z} + \frac{m_{\mathrm{end}}}{z} + m_{\mathrm{cat}} - m_{\mathrm{elec}} \qquad \text{(E-1)}$$

Here m_{mon} is the molar mass of monomer repeat unit, n is the number of monomer repeat units, m_{end} is the total molar mass of end groups, m_{cat} is the molar mass of the cation, m_{elec} is the mass of an electron, and z is the number of charge.

In this work, only singly charged ion peaks ($z = 1$) were observed. Rooij et al. introduced two approaches, namely regression and averaging, for determining end group masses.[19] In general, an end group mass is determined by using all measured monoisotopic m/z values in each series. In this work, the resolution in the MALDI−TOF mass spectra decreases and hence so does the mass accuracy of the monoisotopic peaks, as m/z value increases. As a result, when the data points in the high m/z region were included, experimental errors were introduced. This effect becomes more significant on using the regression method, which requires an extrapolation to zero monomer repeat unit because a small variation in the high m/z values will result in large deviation in the intercept. However, high resolution and mass accuracy were always obtained for the ion peaks in the most intensive regions. Therefore, the 10 most intense ion peaks of each series were used for calculating the experimental end group masses in the current work. Treatment of the major series of peaks (peaks I) using the regression method yields a value for the total mass of the end groups of 85.49 ± 0.08 g mol^{-1} and the averaging method gave a value of 85.87 ± 0.08 g mol^{-1}. These values are in good agreement with the theoretical monoisotopic value of 86.07 for oligoNVPs with α-3-methylbutan-2-on-3-yl,ω-H functionality.

Several other initiation and termination events can also be envisaged in these polymerizations. First, initiation by primary radicals will lead to the formation of oligomers with initiator fragments as the end group. The calculated end group mass (m_{end}) for the series of peaks labeled VII in Figure 1 is 68.73 ± 0.04. This value is equivalent to the sum of the monoisotopic masses of α-2-cyanoprop-2-yl (the radical derived from an AIBN homolytic fragmentation) and ω-H end groups (69.06 g mol^{-1}). In Table 1, a measured monoisotopic m/z of the series of peaks VII is compared with a theoretical value of AIBN fragment mono-functionalized oligoNVP consisting of 19 NVP repeat units. This assignment was confirmed by the increase in the relative intensity of this series of peaks in the MALDI−TOF mass spectrum with increased AIBN concentration.

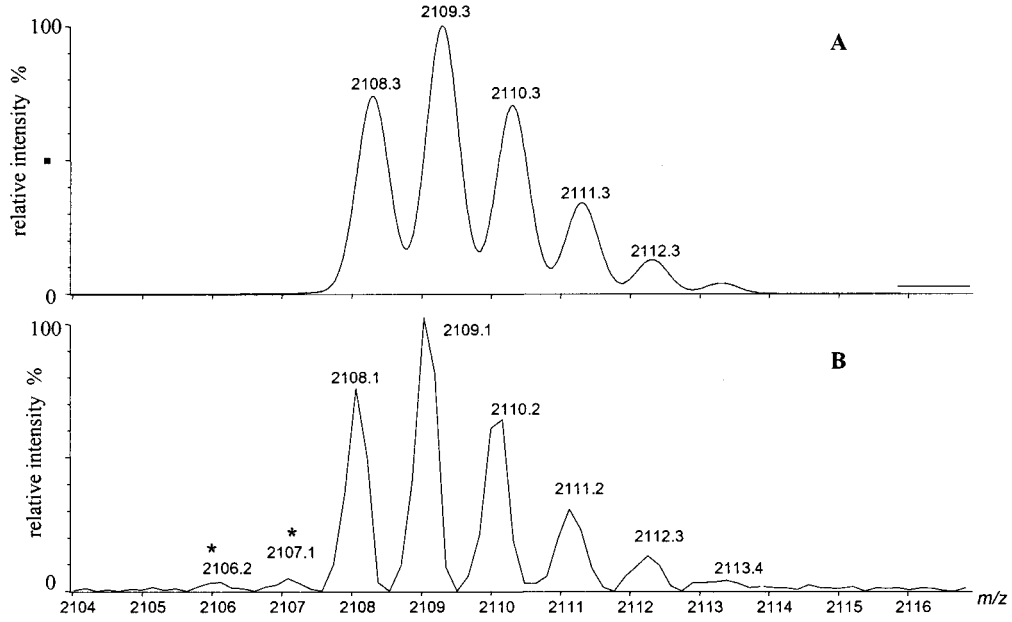
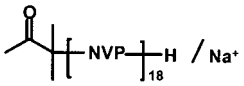
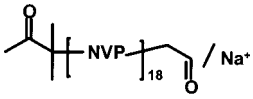
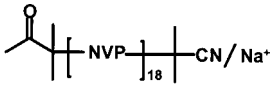
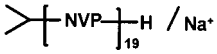
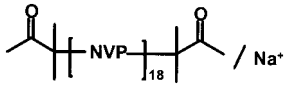
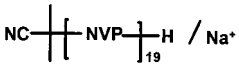


Figure 2. Comparison between simulation and experimental isotopic patterns for the peaks I in Figure 1: (A) simulated isotopic distribution of oligoNVPs with α-3-methylbutan-2-only, ω-H, consisting of 18 NVP repeat units; (B) experimental isotopic distribution.

Table 1. MALDI−TOF MS Experimental Values for AIBN-Initiated OligoNVPs[a]

peaks	adducts[b]	*m/z* theor[c]	*m/z* expt[c]	m_{end} averaging	m_{end} regression
I		2108.3	2108.1	85.9 ± 0.1	85.5 ± 0.1
II	[d]			99.7 ± 0.1	99.5 ± 0.1
III				110.8 ± 0.1	110.7 ± 0.1
IV		2150.3	2150.1	127.9 ± 0.1	127.7 ± 0.1
Va		2175.3	2175.1	152.9 ± 0.1	152.8 ± 0.1
Vb		2177.4	2177.1	43.8 ± 0.1	43.5 ± 0.1
VI		2192.4	2192.2	169.9 ± 0.1	169.8 ± 0.1
VII		2202.4	2202.1	68.9 ± 0.0	68.7 ± 0.1

[a] All masses are monoisotopic values. [b] NVP in the structural formula represents NVP repeat unit. [c] Examples of assigned peaks. [d] Not assigned.

Bimolecular terminations will also generate different end groups. Thus disproportionation generates two macromolecules (reaction 13 in Scheme 2). One of which has a structure identical to that formed by chain transfer to MB and the other has an unsaturated group at the ω end and differs in mass, from the oligomers with α-3-methylbutan-2-on-3-yl, ω-H chain ends, by 2 g mol^{-1}. Therefore, the two peaks at low *m/z*, identified in Figure 2, could be derived from the isotopic distribution of this species. Termination by combination with either the 3-methylbutan-2-on-3-yl radical or another propagating oligomeric radical will generate oligomers with 3-methylbutan-2-on-3-yl groups at both α- and ω-chain ends. The series of peaks VI has a calculated m_{end} of 169.82 ± 0.05 g mol^{-1}, which is consistent with an assignment to oligomers with bis(α−ω-3-methylbutan-2-only) end groups (2 × 85.06 = 170.12 g mol^{-1}). Comparison between one measured monoisotopic *m/z* and a theoretical value is presented in Table 1.

Since we have shown above that initiation by the 2-cyanoprop-2-yl radical and bimolecular terminations occur to a small degree in these systems, one should also expect to observe oligomers with α-3-methylbutan-2-on-3-yl, ω-2-cyanoprop-2-yl and with bis(α,ω-2-cyanoprop-2-yl) end groups. A simulation of the isotopic distribution of oligoNVPs with α-3-methylbutan-2-on-3-yl, ω-2-cyanoprop-2-yl end groups and consisting of 18 NVP repeat units partially matches the peaks V in

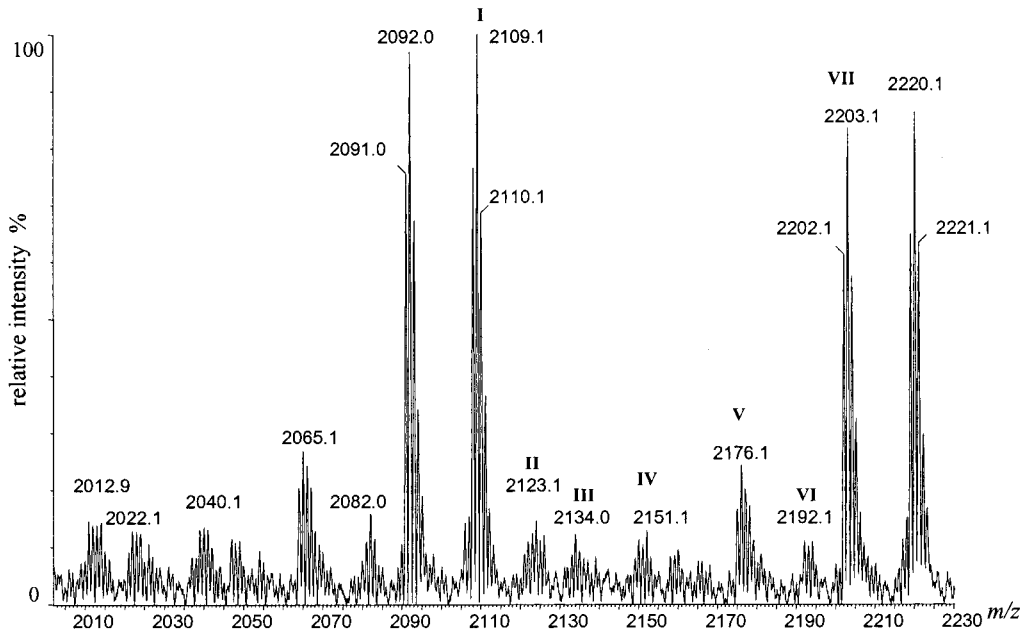


Figure 3. Expansion of MALDI−TOF mass spectrum of oligoNVP synthesized by using increased concentration of AIBN. molar ratio in feed: NVP:AIBN:MB = 100:3.3:636.

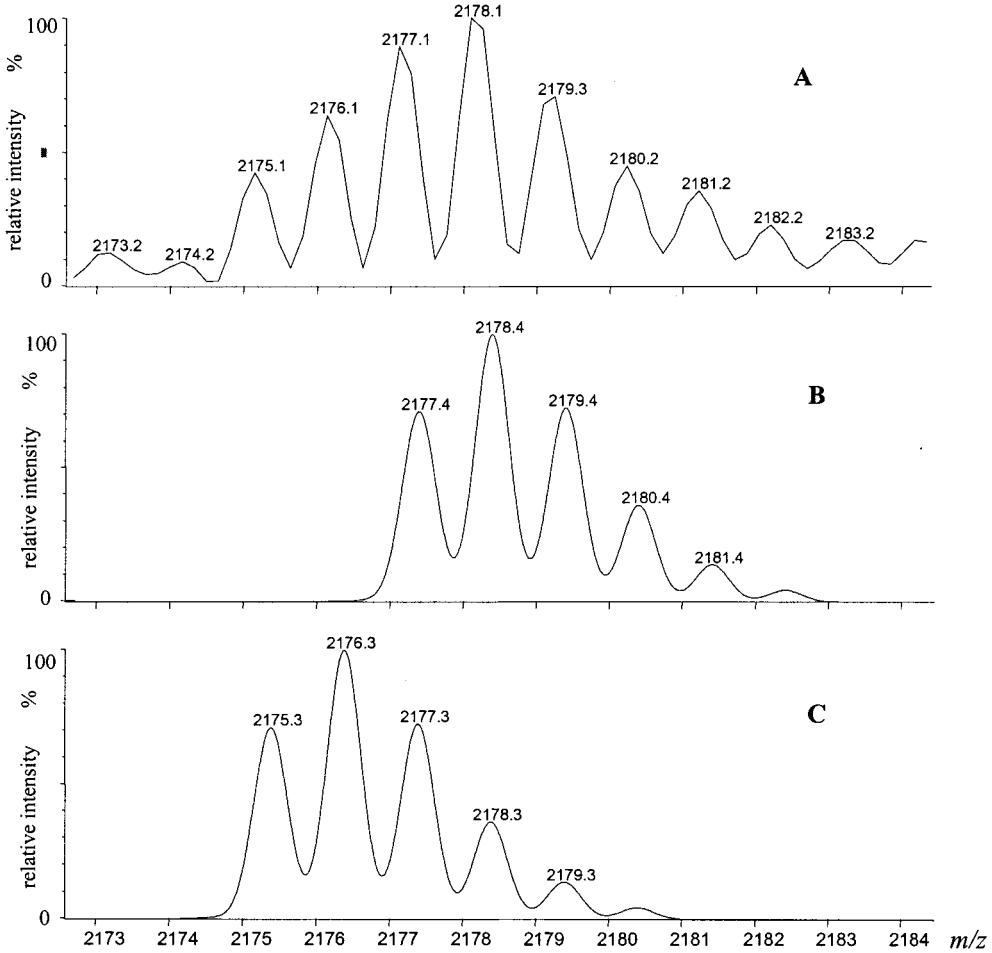


Figure 4. Comparison between simulation and experimental isotopic patterns for the peaks V in Figure 2: (A) experimental isotopic distribution; (B) simulation of isotopic oligoNVPs with α-isopropyl, ω-H, consisting of 19 NVP repeat units; (C) simulation of isotopic oligoNVPs with α-3-methylbutan-2-onyl, ω-cyanopropanyl, consisting of 18 NVP repeat units.

Figure 1 (see Figure 4, A and C). This suggests that the isotopic distribution of oligoNVPs with α-3-methylbutan-2-on-3-yl, ω-2-cyanoprop-2-yl end groups overlaps with isotopic signals arising from oligoNVPs with different end groups. Also the relative intensity of the isotopic signals at low *m*/*z* values in the peaks V significantly increased with increased AIBN concentration in the polymerization. However, peaks that could

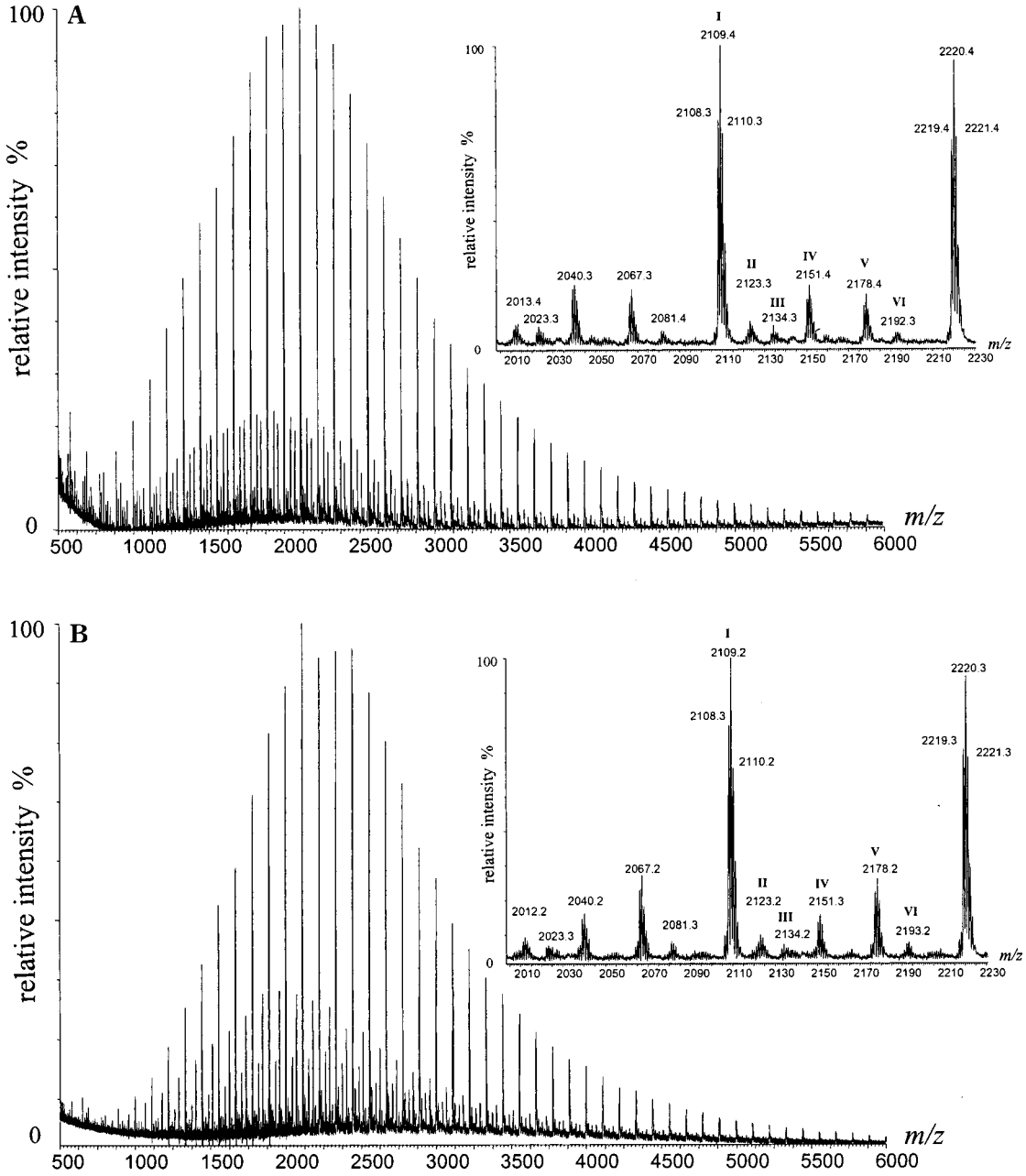


Figure 5. MALDI−TOF mass spectra of BPO and CHP initiated oligoNVPs: (A) molar ratio in feed, NVP:BPO:MB = 100:0.52:731; (B) molar ratio in feed:, NVP:CHP:MB = 100:0.65:677.

be assigned to the oligoNVPs with bis(α,ω-2-cyanoprop-2-yl) end groups were not observed probably because they were produced in very low concentration.

To further investigate the assignment of the end groups corresponding to the other minor peaks in Figure 1, oligoNVPs were synthesized separately by using either CHP or BPO as initiators. The MALDI−TOF mass spectra and the expansions of the two types of oligoNVPs are shown in Figure 5, parts A and B, respectively. It is clear that the series of ion peaks I−VI in the spectrum of oligoNVPs derived from polymerizations initiated by AIBN are also present in the spectra of the other two oligoNVP samples. However, the peaks associated with initiation by the 2-cyanoprop-2-yl radical (peaks VII in the mass spectra derived from oligoNVPs initiated by AIBN) are absent. The presence of series of peaks I−VI in the three spectra confirms that none of these series of peaks can be solely assigned to any sodium ionadducts of oligoNVPs with end group derived from either AIBN, CHP, or BPO initiator fragments. Also, the MALDI−TOF mass spectra of the oligoNVP samples obtained by using potassium as a cationization agent are identical to those shown in Figures 1 and 5, except that the corresponding series of peaks differ by m/z = 16 g mol^{-1}. Therefore, these series of peaks are not due to the adducts formed with other adventitious cations.

Figure 6A shows a typical ^{1}H NMR spectrum of a product of polymerization of NVP in MB using AIBN as the initiator. A spectrum of PNVP prepared by bulk polymerization is also shown in Figure 6B for comparison. As expected, signals due to the methyl end group protons are clearly observed in spectrum 6A. The signals at around 0.9 and 1.3 ppm suggest the presence of multiple chain end functionalities. The two signals are due to the methyl groups of the chain end that are derived from the isopropyl group of the solvent. Also, a

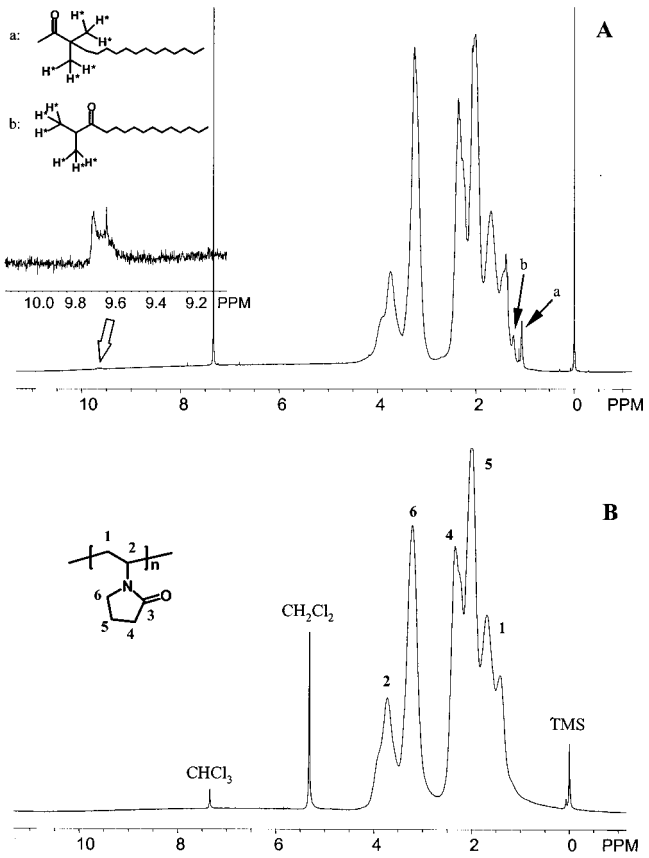


Figure 6. ^{1}H NMR spectra of oligoNVPs: (A**)** molar ratio in feed: NVP:AIBN:MB = 100:1.4:1293; (B) prepared by bulk polymerization at 70 °C, NVP:AIBN = 100:0.68 (mol/mol).

small broad signal is observed around 9.7 ppm in the ^{1}H NMR spectra of the samples (see Figure 6A): an implication of an aldehyde end group. On the basis of these results, it is postulated that transfer of hydrogen from the 1-methyl group of MB rather than the isopropyl group can also occur (see reaction 3 in Scheme 2). These radicals can then initiate polymerization and give rise to end groups with the same mass as the dominant series. However, the chain-end methyl groups will be different and they produce two separate chemical shifts in the NMR spectra. Thus, initiation from the 1-methyl group of MB will lead to the α-3-methylbutan-2-on-1-yl end group while initiation from the isopropyl position of MB will lead to the α-3-methylbutan-2-on-3-yl end group (reactions 5 and 6 in Scheme 2) and the methyl hydrogens of the latter end group will lie downfield of those of the former end group. Predictions of the chemical shifts of these two end groups were run and resulted in chemical shifts for methyl protons derived from the isopropyl group of MB of 1.1 ppm for the end group resulting from initiation by the α-3-methylbutan-2-on-1-yl radical and 1.2 for initiation by the α-3-methylbutan-2-on-3-yl radical. Abstraction at the 1-methyl group produces a primary radical stabilized by resonance with the ketone group. However, primary radical species are usually less stable than the similar tertiary radicals[21] so that it is feasible that this species may fragment as shown in reaction 4 in Scheme 2 giving an isopropyl radical and a ketene. The isopropyl radicals would initiate to form oligoNVPs with isopropyl end groups (reaction 7 in Scheme 2). The simulated MS isotopic pattern of an oligoNVP sample with α-isopropyl and ω-H end groups and consisting of 19 NVP repeat units is shown in Figure 4B. Combination of the two simulations, derived from the latter chain and the chain referred to previously with α-3-methylbutan-2-on-3-yl and ω-2-cyanoprop-2-yl end groups, matches the experimentally observed distribution shown in Figure 4A. It is possible that a ketene molecule could be attacked by a propagating radical[22] (reaction 10 in Scheme 2) and the newly formed oligomeric radical would probably transfer to MB, leading to the formation of oligoNVP with an acetaldehyde group at the ω end (reaction 12 in Scheme 2). The *m*/*z* of the series of peaks IV is in good accord with the theoretical value of the sodium ion adduct of an oligoNVP with α-3-methylbutan-2-on-3-yl, ω-acetaldehyde end groups (see Table 1).

The calculated m_{end} values for the peaks II and III are 99.86 ± 0.10 and 110.84 ± 0.06, respectively. They cannot be assigned to any oligoNVPs with end groups formed in the current schemes of polymerization and probably arise from chain fragmentation in the MALDI process, a phenomenon that has previously been reported in the literature.[15, 20]

Conclusion

On the basis of the end group analysis discussed in the preceding sections, it is possible to identify the key reactions in the free radical polymerizations of NVP in MB (see Scheme 2). The majority of the oligoNVPs have the α-3-methylbutan-2-on-3-yl, ω-H chain-end structure, but as expected, several other simultaneous events produce chains with other end groups. Initially, we expected that the inevitable initiation by the primary radical would be the main event that would produce chains with end groups other than α-3-methylbutan-2-on-3-yl, ω-H but surprisingly initiation following abstraction at the 1-methyl position also occurs as does fragmentation of this radical. This latter reaction leads to the formation of small amounts of acetaldehyde and isopropyl end groups.

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