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Synthesis and polymerization of new multifunctional pyrrolidinone methacrylate monomers

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ABSTRACT

Methacrylate monomers have been widely used in medical and dental applications such as bone cements, dental fillings, bioadhesives, and hydrogels. One major problem of these monomers resides in their low rates of polymerization leading to leaching problems that cause irritation of the surrounding tissues and even cell death. Here we describe the synthesis and polymerization of new mono-methacrylates containing multifunctional pyrrolidinone moieties. Such monomers possess stronger inherent hydrogen bonding potential susceptible to increase their reactivity and polymerization rates. These monomers were shown to homopolymerize rapidly leading to crosslinked polymers. The corresponding rates of polymerization were found to be comparable to difunctional methacrylates such as hexanediol dimethacrylate. Intermolecular hydrogen bonding interactions involving the pyrrolidinone unit leads these monomers to behave as "pseudo" difunctional monomers upon homopolymerization.

1. Introduction

Methacrylate monomers have found broad use in medical and dental applications such as bone cements, dental fillings, bioadhesives, and hydrogels [1–6]. One major problem attached to many of these methacrylate derivatives resides in their low rates of polymerization leading to leaching problems that cause irritation of the surrounding tissues and even cell death [7]. Incorporation of pendant groups that enhance the polymerization rates while not reducing the inherent adhesion properties of acrylate-based systems is required in many applications [8–10].

Bowman, Jansen, and Decker have demonstrated that both intermolecular interactions, such as hydrogen bonding, aromatic and heterocyclic ring stacking, and specific intramolecular effects have a significant effect on the polymerization activity of methacrylates [11–14]. Hoyle, et al., also illustrated the effect of hydrogen bonding on the overall rate of polymerization of methacrylate monomers [15]. In the case of hydrogen bonding monomers, the rate is increased since the monomers mimic covalently bonded multifunctional monomers which have much faster rates than monofunctional monomers due to reduced termination rates [12,15]. High rates of polymerization and conversion lead to a reduction in unreacted leachable monomer from these systems. Larger pendent groups can also increase glass transition temperatures (T_gs) and reduce shrinkage of the copolymer systems usually used in biomaterial applications.

Alkyl α-hydroxymethylacrylate is one example of chemistry that enable tailoring of both polymerizability and final polymer properties [10,16–17]. For example, conversion of the hydroxymethyl group to ester groups was found to dramatically increase rates of polymerization [18]. Recently we reported extremely high Michael addition reactivities of alkyl 2-(carboethoxyhydroxymethyl)acrylates upon reaction with primary amines leading to a simple, mild and efficient route for the preparation of new polyfunctional pyrrolidinones and pyrrolidinone methacrylate monomers [19].

Herein we report the synthesis, polymerization and characterization of new methacrylate monomers incorporating pyrrolidinone pendant groups capable of strong hydrogen bonding interactions (Fig. 1). Optically active 2-pyrrolidinone compounds have found applications in a lot of domains ranging from biology to biochemistry and pharmaceutics. Results from two different systems, one incorporating a pyrrolidinone unit as a second functionality and the other incorporating an analog pyrrolidinone unit bound to an R-hydroxymethacrylate monomer through an ester linkage, are reported here.

2. Experimental

2.1. Materials

n-Butyl methacrylate (BMA), methyl acrylate, 1,6-hexanediol dimethacrylate (HDDMA), *N*-vinylpyrrolidone, 2-hydroxyethyl

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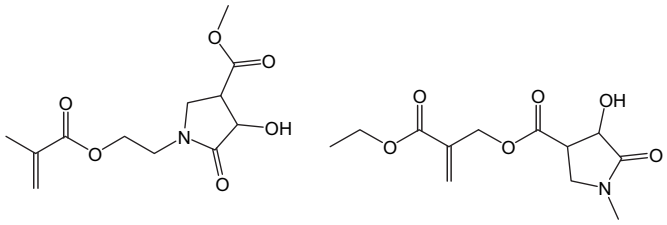


Monomer 3 **Monomer 4**

Fig. 1. Structures of 2-pyrrolidinone-containing monomers **3** and **4**.

methacrylate (HEMA), 4-diaza[2.2.2]bicyclooctane (DABCO), and methylamine (40 wt% in water) were obtained from Aldrich Chemical and used as received. 2,2′-Azobis(2-methylpropionitrile) (AIBN) was purchased from Aldrich Chemical and recrystalized from methanol before use. Ethyl glyoxylate (50 wt% in toluene) was purchased from Alfa Aesar Chemical and used as received. 2-Hydroxy-2-methyl-1-phenyl-1-propanone (Darocur 1173) was obtained from Ciba and used as the photoinitiator. Ethyl α-hydroxyl methylacrylate (EHMA) was donated by Nippon Shokubai Co., Tokyo, Japan. Ethyl α-chloromethyl acrylate (ECMA) was synthesized from EHMA according to a previously reported literature method [20].

2.2. Preparation of methyl 2-(carboethoxyhydroxymethyl)-acrylate 1 [19]

Ethyl glyoxylate, 50 wt% in toluene (20.39 g, 199.7 mmol), DABCO (3.64 g, 32.4 mmol) and methyl acrylate (17.19 g, 199.7 mmol) were added with stirring to a 250 mL round bottom flask. The reaction began immediately and was slightly exothermic. The mixture was stirred at room temperature for 2 h. The crude solution was then concentrated under reduced pressure. The resulting mixture was washed with 3 aliquots of sodium chloride solution followed by 3 aliquots of deionized water. The organic phase was then dried over a bed of sodium sulfate and vacuum distillation of the residue gave methyl 2-(carboethoxyhydroxymethyl)acrylate **1** as a clear liquid in ca 68% yield (bp 135–137 °C (20 mm Hg)).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, $-CH_3$), 3.68 (s, H, –OH), 3.78 (s, 3H, $-OCH_3$), 4.26 (q, 2H, $-CH_2CH_3$), 4.88 (s, H, –CHOH), 5.96 and 6.37 (s, 2H, $-CH_2$=C); ^{13}C NMR ($CDCl_3$) δ 14.04 ($-CH_3$), 52.12 (–OCH3), 62.20 ($-CH_2CH_3$), 71.19 (–CHOH), 128.96 (CH_2=C), 138.08 (C=CH_2), 165.68 and 172.30 (C=O). FT-IR (neat, cm^{-1}) 3515, 2996, 1739, 1643, 1446, 1097, 823. Anal. Calcd for C8H15O5·0.25*H_2O: C, 50.59; H, 6.49. Found: C, 50.28; H, 6.28.

2.3. Preparation of methyl 1-methyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate 2

Compound **1** (10 g, 53.14 mmol) was added to a 50 ml tube equipped with an argon gas inlet. The reaction tube was then purged with argon for 30 min and sealed with a rubber septum. Methylamine (40 wt% in water) was added dropwise in slight excess (5.48 g, 54.21 mmol) to the mixture and the resulting solution was allowed to stir for 24 h at room temperature. Upon reaction completion as monitored by ^{1}H NMR, the solvent was removed under reduced pressure. Once concentrated, the crude product was purified by distilling off the excess amine to give methyl 1-methyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2** as a brown oil in ca 96% yield and as a mixture of two stereoisomers (A and B, mole ratio 42:58).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $-CH_3$), 1.28 (m, 2H, $-CH_2$), 1.52 (m, 2H, $-CH_2CH_2N$), 3.74$_{(A)}$ and 3.77$_{(B)}$ (s, 3H, $-CH_3$), 4.59$_{(A)}$ and 4.60$_{(B)}$ (d, H, –CHOH); ^{13}C NMR ($CDCl_3$) δ 14.17$_{(A+B)}$ ($-CH_3$), 22.52$_{(A+B)}$ ($-CH_2CH_3$), 26.38 and 26.85 ($-CH_2CH_2CH_3$), 31.41 and 31.44 ($-CH_2CH_3$), 42.96 and 43.04 ($-CH_2N$), 43.07 and 45.62 ($-CHCH_2N$), 46.07 and 46.29 ($-CH_2N$), 52.16 and 52.53 ($-OCH_3$), 70.46 and 72.43 (–CHOH), 170.74 and 172.25 (C=O), 172.82 and 173.09 (NC=O). FT-IR (neat, cm^{-1}) 3363, 2958, 2935, 2866, 1741, 1695, 1278, 740. Anal. Calcd for C12H21NO4: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.42; H, 8.71; N, 5.84.

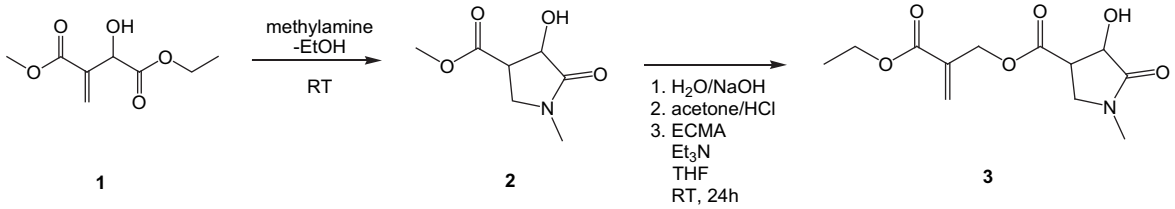
2.4. Preparation of 4-hydroxy-1-methyl-5-oxopyrrolidine-3-carboxylic acid 2′

Methyl 1-methyl-4-hydroxy-5-oxopyrrolidine-3-carboxylate **2** was first treated with 1 equivalent of sodium hydroxide in 10 ml of deionized water. The resulting mixture was allowed to stir for 1 h before precipitating it in 80 ml of acetone. The white salt formed was then filtered off, re-dispersed in 50 ml of acetone and treated with dilute hydrochloric acid. The precipitate was filtered off and dried under reduced pressure to afford 4-hydroxy-1-methyl-5-oxopyrrolidine-3-carboxylic acid **2′** as a white powder in ca 96% yield as a mixture of two stereoisomers (A and B, mole ratio. 42:58).

2.5. Synthesis of monomer 3

ECMA (2 g, 13.45 mmol), 4-hydroxy-1-methyl-5-oxopyrrolidine-3-carboxylic acid **2′** (2.86 g, 13.45 mmol) and triethylamine (1.36 g, 13.45 mmol) were added to 15 ml of dry THF. The resulting mixture was allowed to stir for 24 h at room temperature. The white precipitate was filtered off and the crude solution concentrated under reduced pressure to give monomer **3** as brown oil and in ca 76% yield.

^{1}H NMR (300 MHz, $CDCl_3$) d 0.88 (t, 3H, $-CH_3$), 1.28 (m, 2H, $-CH_2$), 1.52 (m, 2H, $-CH_2CH_2N$), 4.25 300 (q, 2H, $-CH_2CH_3$), 4.59 (d, H, –CHOH), 4.91 (s, 2H, $-CH_2O$), 5.91 and 6.39 (s, 2H, CH_2=C); ^{13}C NMR ($CDCl_3$) d 14.01 ($-CH_3$), 14.17 ($-CH_3$), 22.49 ($-CH_2CH_3$), 31.40 ($-CH_2CH_2CH_3$), 26.38 ($-CH_2CH_2CH_2N$), 26.93 ($-CH_2CH_2N$), 46.17 ($-CH_2N$), 43.07 ($-CHCH_2N$), 45.46 ($-CH_2N$), 61.12 ($-CH_2CH_3$), 63.34 ($-CH_2O$), 72.40 (–CHOH), 127.84 ($-CH_2$=C), 134.86 ($-CCH_2$), 165.04 and 171.11 (–C=O), 172.72 (–NCO). FT-IR (NaCl, cm^{-1}) 3351, 2960, 2935, 2870, 1741, 1729, 1685, 1654, 1277, 819.



Scheme 1. Synthesis of monomer **3**.

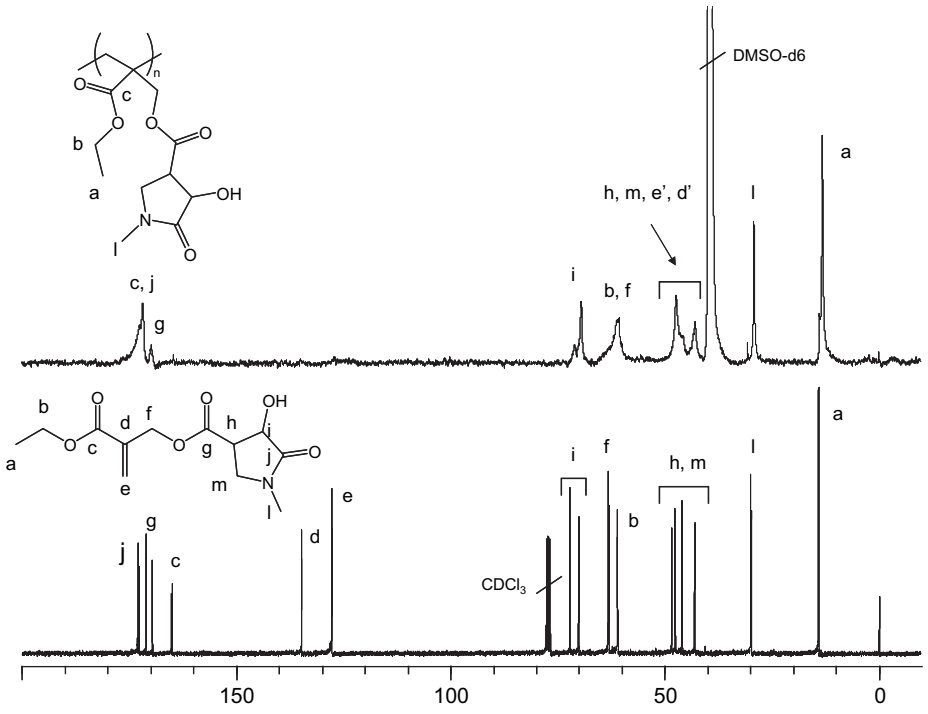


Fig. 2. ^{13}C NMR spectra of monomer **3** ($CDCl_3$) and the corresponding homopolymer PyP1 (DMSO-d_6).

2.6. Synthesis of monomer 4

2-Aminoethyl methacrylate hydrochloride (5 g, 30.18 mmol) and **1** (5.67 g, 30.18 mmol) were added to 50 ml of dry THF in a 250 ml round bottom flask placed in a ice/acetone bath. Triethylamine (3.54 g, 35 mmol) was then added dropwise to the stirring mixture. The resulting solution was allowed to stir until the temperature reached room temperature. The mixture was stirred for 12 more hours. The crude solution was then precipitated in cold diethyl ether. The white precipitate was filtered off and the crude solution concentrated under reduced pressure. The resulting brown oil was washed 3 times with *n*-hexane and dried under reduced pressure to afford monomer **4** as a brown oil as a mixture of two stereoisomers (A and B, mole ratio 50:50) in ca 82% yield.

^1H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3H, $-CH_3$), $3.74_{(A)}$ and $3.78_{(B)}$ (s, 3H, $-CH_3$), $5.60_{(A)}$ and $5.61_{(B)}$ (s, 1H, $-CH_2{=}C$), $6.10_{(A)}$ and $6.11_{(B)}$ (s, 1H, $-CH_2{=}C$); ^{13}C NMR ($CDCl_3$) δ $18.31_{(A+B)}$ ($-CH_3$), $42.15_{(A)}$ and $43.23_{(B)}$ ($-CH_2N$), $42.24_{(A)}$ and $4.17_{(B)}$ ($-CHCH_2N$), $46.51_{(A)}$ and $47.28_{(B)}$ ($-CH_2N$), $52.27_{(A)}$ and $52.62_{(B)}$ ($-OCH_3$), $70.16_{(A)}$ and 72.08 ($-CHOH$), $126.36_{(A)}$ and $126.41_{(B)}$ ($-CH_2C$), $135.70_{(A)}$ and $135.76_{(A)}$ ($-CCH_2$), $166.98_{(A)}$ and $167.05_{(B)}$ (C=O), $170.57_{(A)}$ and $173.07_{(B)}$ (C=O), $171.91_{(A)}$ and $173.41_{(B)}$ (NC=O).

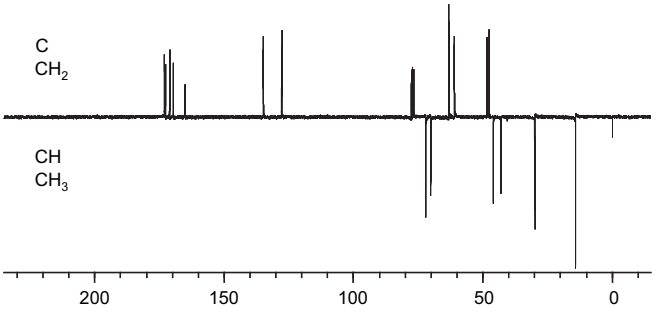
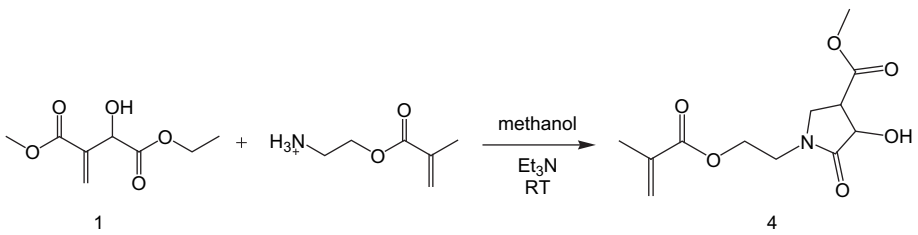


Fig. 3. APT spectrum of monomer 3 ($CDCl_3$).

2.7. Analysis

Solution ^1H and ^{13}C NMR spectra of the intermediates and monomers were collected on a Bruker AC-300 MHz spectrometer at room temperature using $CDCl_3$ with TMS as an internal reference. Solution ^{13}C NMR spectra of the polymers were collected on a INOVA 500 MHz spectrometer at room temperature using DMSO-d_6 with TMS as an internal reference.

Infrared spectra were obtained using a Galaxies series 5000 Fourier transform infrared spectrometer (Mattson). Real-time infrared (RTIR) spectra were recorded on a modified Bruker 88



Scheme 2. Synthesis of monomer **4**.

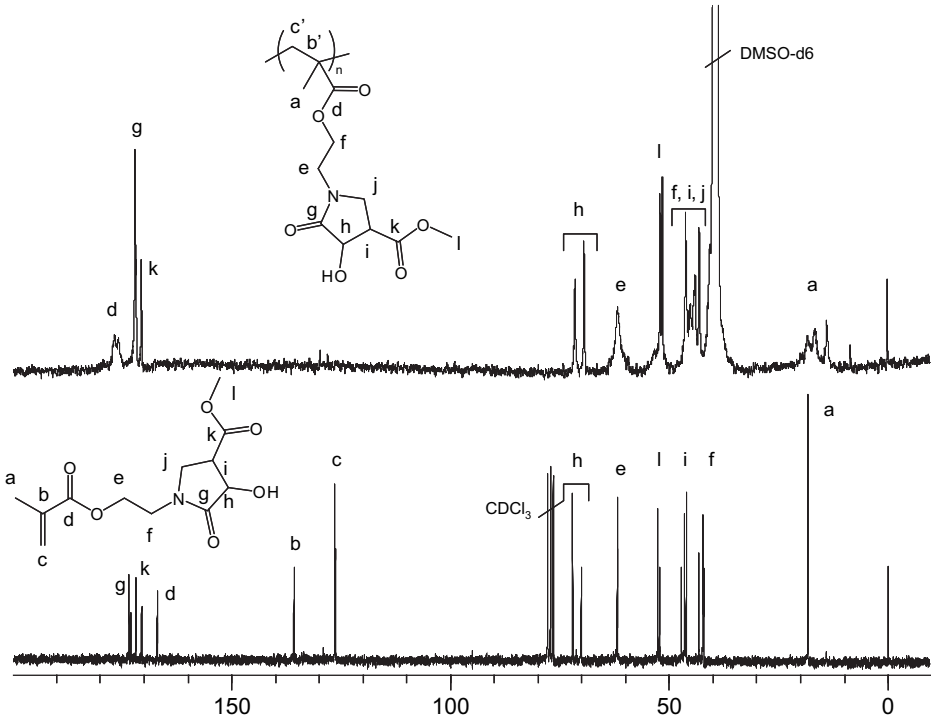


Fig. 4. ^{13}C NMR spectra of monomer 4 ($CDCl_3$) and the corresponding homopolymer PyP2 (DMSO-*d*6).

spectrometer. UV light from an Oriel lamp system equipped with a 200-W, high-pressure mercury-xenon bulb was channeled through an electric shutter and fiber optic cable in the sample chamber filled with dry air. The photopolymerizations were conducted in a cell prepared by sandwiching the samples between two sodium chloride salt plates with a thickness of approximately 20 μm. Photopolymerizations were conducted upon exposure to the UV light at an intensity of 11.4 mW/cm^2. (The light intensity was measured with an IL-1400 calibrated radiometer from International Light.) Infrared absorption spectra were obtained under continuous UV irradiation at a scanning rate of 5 scans per second. Darocur 1173 3 wt% was used as initiator. The characteristic infrared absorbance band (812 cm^{-1}) was used to monitor the disappearance of the monomers during the photoreactions.

3. Results and discussion

3.1. Monomers preparation

First, methyl 2-(carboethoxyhydroxymethyl)acrylate **1** was synthesized following a procedure reported previously [20]. Monomer **3** was synthesized in two steps from pyrrolidinone **2** and ECMA with an overall yield of 76% and 98% purity as determined by HPLC analysis (Scheme 1). The monomer was soluble in water, chloroform, methanol, ethyl acetate, methylene chloride and tetrahydrofuran.

The ^{13}C NMR spectrum of monomer **3** is shown in Fig. 2 along with the spectrum of the polymer. Attached Proton Test (APT) analysis allowed the accurate assignment of each peak (Fig. 3).

Monomer **4**, soluble in the same solvents as monomer **3**, was synthesized in one step from methyl 2-(carboethoxyhydroxymethyl)acrylate **1** and 2-aminoethyl methacrylate hydrochloride in the presence of triethylamine (Scheme 2) with an overall yield of 82% (95% purity) as determined by ^1H NMR analysis. The ^{13}C NMR spectrum is shown in Fig. 4, confirming its structure; the spectrum of its polymer is included for comparison. 2-Aminoethyl methacrylate hydrochloride suffers from intramolecular rearrangements upon deprotonation. The high yield of monomer **4** at room temperature testifies to a highly efficient Michael addition. This unusual high reactivity allows minimization of any side reaction via rearrangement that might otherwise occur. Hence, it can be concluded that a unique combination of intra- and intermolecular hydrogen bonding interactions leads to extremely rapid formation of pyrrolidinone compounds as exhibited by the formation of monomer **4**.

3.2. Photopolymerization

The steady-state polymerization kinetics of monomers 3 and 4 was investigated using photoinitiation and real-time infrared spectroscopy (RTIR). Results were compared to standard mono- and dimethacrylated systems (Fig. 5).

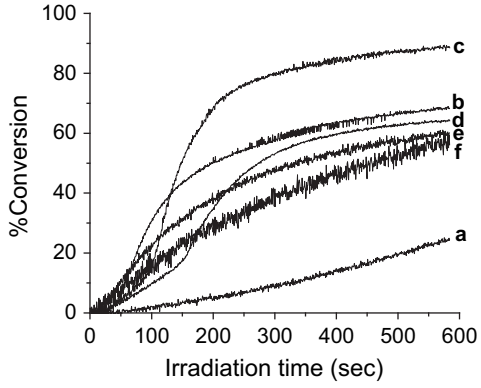
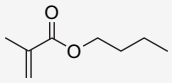
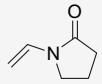
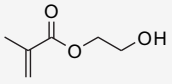
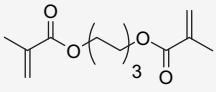
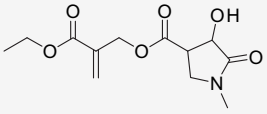
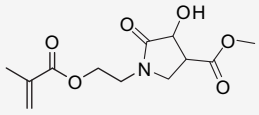


Fig. 5. Conversion as a function of time for BMA (a), HDDMA (b), HEMA (c), NVP (d), monomer 3 (e), and monomer 4 (f).

Table 1
Kinetic analysis of methacrylate monomers at 25 °C.

Monomer	Moles/L[a]	R_p (s^{-1})[b]	Conversion (%)[c]
 BMA	6.3	0.0006	24
 *N*-vinylpyrrolidone	9.4	0.0036	64
 HEMA	8.2	0.0091	88
 HDDMA	7.8	0.008	68
 Monomer **3**	4.6	0.0014	56
 Monomer **4**	4.4	0.0024	60

[a] Initial double bond concentration.
[b] Normalized measurement of the maximum polymerization rate.
[c] Maximum conversion reached after 600 s of irradiation at ambient conditions.

The monomer structures and kinetic data extracted from RTIR results are presented in Table 1. Both the rates and extents of conversion for monomers **3** and **4** are much greater than those for butyl methacrylate and approach those of the difunctional monomer, 1,6-hexanediol dimethacrylate.

It is well known that hydrogen bonding is an important parameter that can affect system mobility and organization during polymerization resulting in enhanced rates due to formation of dimer-like species which reduce termination and enhance polymerization kinetics [10]. Conversion profiles for monomers **3** and **4** were shown to be very close to the HDDMA conversion profile suggesting that these monomers behave similarly to multifunctional monomers via intermolecular association as illustrated in Fig. 6. The low conversion values observed after 600 seconds result from polymerization of a dimer-like monomer (Fig. 6) and some degree of chemical crosslinking due apparently to chain transfer to the reactive hydrogen on the pyrrolidinone ring as the resulting polymers were insoluble in DMSO and DMF.

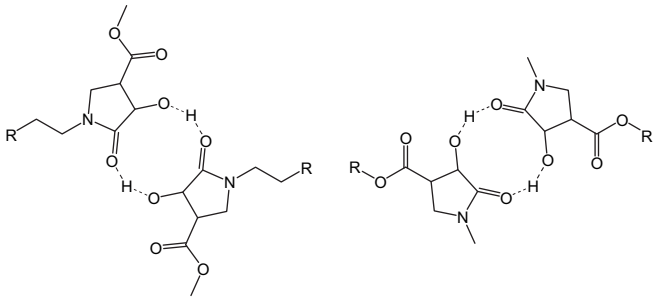


Fig. 6. Proposed molecular associations.

Next, photopolymerization reactions of monomers **3** and **4**, HDDMA and BMA were conducted in *N*-methylpyrrolidone. Results for HEMA, which also forms hydrogen bonds and acts as a pseudodimethacrylate, are given for comparison. As shown in Fig. 7, monomers **3** and **4** polymerize rapidly in *N*-methylpyrrolidone, a little slower than HDDMA, but much faster than BMA. Again, these results are consistent with the structures shown in Fig. 6.

3.3. Solution free radical polymerization

The pyrrolidinone-containing monomers were polymerized in DMSO under argon atmosphere using AIBN as thermal initiator (0.1 mol%) at 65 °C. Both polymers were highly soluble in DMSO while initial attempts to polymerize monomers **3** and **4** in methanol and tetrahydrofuran gave low yields. The polymers were precipitated in acetone and dried under reduced pressure before any characterization: the homopolymers **PyP1** and **PyP2** correspond to the polymerization of monomer **3** and monomer **4,** respectively. ^{13}C NMR spectra of the monomers along with those of their polymers obtained by solution polymerization in DMSO are shown in Figs. 2 and 4.

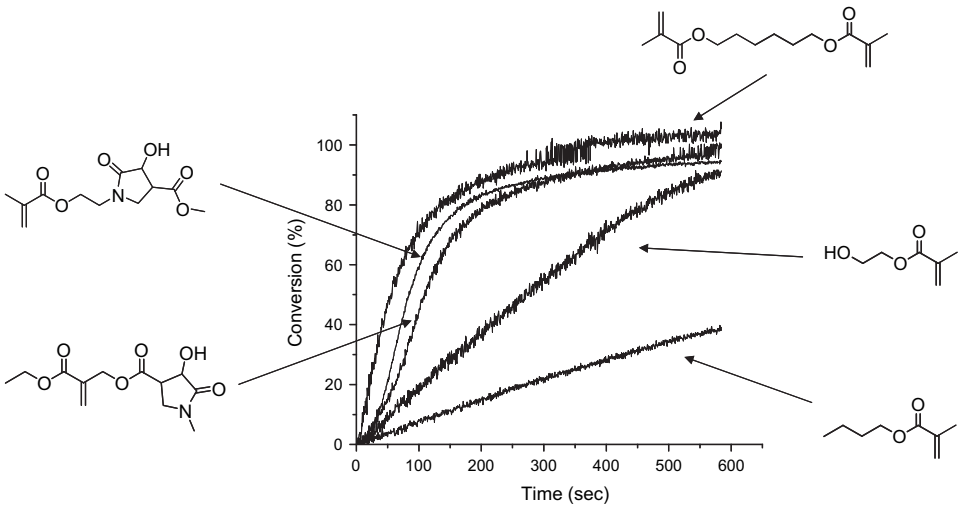


Fig. 7. Conversion as a function of time for BMA (a), HDDMA (b), HEMA (c), NVP (d), monomer **3** (e), and monomer **4** (f) in NMP (50/50).

4. Conclusions

New multifunctional pyrrolidinone-containing methacrylate monomers were synthesized successfully. These monomers display rates of polymerization comparable to difunctional methacrylates such as hexanediol dimethacrylate. Intermolecular hydrogen bonding interactions involving the pyrrolidinone unit leads these monomers to behave as ''pseudo'' difunctional monomers upon homopolymerization. These new monomers open up a new pathway for synthesis of pyrrolidinone compounds that have the potential of being incorporated into materials with applications, for example, in the biomedical field. For instance strong hydrogen bridges can lead to improved mechanical properties and adhesion in dental material formulations.

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