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Unexpected Transesterification of Tertiary Amine Methacrylates during Methanolic ATRP at Ambient Temperature: A Cautionary Tale

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Introduction

In the past few years, atom transfer radical polymerization (ATRP)[1,2] has been shown to be a versatile technique for the controlled polymerization of many monomer classes, including acrylates, methacrylates, and styrenics.[3,4] Moreover, this living radical polymerization technique is tolerant of a wide range of functional groups present in the monomer, solvent, or initiator. Although ATRP is usually performed in the bulk or in an organic solvent, the efficient polymerization of various hydrophilic methacrylates in protic media has been recently demonstrated at ambient temperature. Sodium 4-vinylbenzoate (NaVBA),[5] methoxy-capped oligo(ethylene glycol) methacrylate (OEGMA),[6] sodium methacrylate (NaMAA),[7] and 2-(dimethylamino)ethyl methacrylate (DMA)[8] have been successfully polymerized via aqueous ATRP. Under these conditions the polymerizations are fairly fast (complete conversion can be achieved within 1 h), which leads to reduced control over the molecular weight distribution ($M_w/M_n = 1.3-1.4$).

Polymerizations carried out in either water/alcohol mixtures or pure alcohol lead to significantly slower rates and hence better control. Thus, the controlled polymerization of 2-hydroxyethyl methacrylate (HEMA) was achieved by Robinson et al. using ATRP in methanol/water mixtures or in pure methanol at 20 °C. Polydispersities were around 1.1−1.2 for polymerizations in methanol and around 1.2−1.3 for syntheses in 50:50 methanol/water mixtures, indicating good living character.[9] More recently, Save et al. investigated the homopolymerization of glycerol monomethacrylate (GMA) and 2-hydroxypropyl methacrylate (HPMA) in protic media. In pure methanol both monomers could be polymerized to high conversion with very good control ($M_w/M_n = 1.1-1.2$), whereas in 50:50 methanol/water mixtures only HPMA could be polymerized in a controlled fashion. In contrast, GMA homopolymers synthesized in the presence of water had relatively high polydispersities ($M_w/M_n = 1.9$).[10]

In light of these promising results for the ATRP of various hydrophilic methacrylates, we recently examined the ATRP of DMA in methanol and methanol/water mixtures at ambient temperature. However, an unforeseen problem was observed for both this basic monomer and also two other tertiary amine methacrylates. In this Note we report that a significant degree of base-catalyzed transesterification can occur in ATRP syntheses conducted in methanol at ambient temperature.

Experimental Section

Materials. 2-(Dimethylamino)ethyl methacrylate (DMA) and 2-(diethylamino)ethyl methacrylate (DEA) were purchased from Aldrich, 2-(diisopropylamino)ethyl methacrylate (DPA) was obtained from Scientific Polymer Products, and 2-(*N*-morpholino)ethyl methacrylate (MEMA) was from Polysciences. Each of these monomers was passed through a basic alumina column to remove inhibitor and stored in a refrigerator before use. All other reagents were purchased from Aldrich and were used as received.

ATRP Syntheses. The typical ATRP protocol was as follows. DMA and methyl α-bromophenylacetate (MBP) initiator were mixed together and degassed by nitrogen purge for 30 min. Methanol and water were degassed separately, and the required amounts of each of these solvents were added successively using syringes. Under nitrogen flow, the Cu(I)-Br/bpy catalyst was then quickly introduced, allowing the reaction to start. The polymerization was terminated by exposing the reaction vessel to air, which led to immediate aerial oxidation of the brown Cu(I) catalyst to give a blue Cu(II) complex, and the polymer was recovered by chloroform extraction. After filtration, the spent Cu(II) catalyst was removed by passing the organic solution through a basic alumina column, and the solvent was evaporated under vacuum.

Transesterification of Tertiary Amine Methacrylates. Under non-ATRP conditions, 8.0 mmol of DMA (or DEA, or DPA, or MEMA) was mixed with 48.0 mmol (3.43 mL) of methanol. Aliquots were regularly taken and diluted in $CDCl_3$ for immediate analysis by ^1H NMR. The remaining tertiary amine methacrylate monomer was quantified by integrating the total vinyl signals between δ 5.5 and δ 6.0 and comparing this with the oxymethylene protons of the tertiary amine methacrylate at δ 4.0−4.1.

Characterization. Molecular weights and molecular weight distributions were assessed by gel permeation chromatography (GPC). The GPC setup consisted of a Perkin-Elmer LC pump and a refractive index detector, with a PLgel 3 μm Mixed-E 300 × 7.5 mm column. Calibration was carried out using nine poly(methyl methacrylate) standards with M_n up to 88 000 g mol^{-1}. The GPC eluent was HPLC grade THF stabilized with BHT that contained 2% (v/v) of triethylamine, at a flow rate of 1.0 mL min^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ using a Bruker Avance DPX 300 spectrometer operating at 300 MHz.

Results and Discussion

Homopolymerizations of DMA were carried out in protic media at ambient temperature using the MBP initiator previously reported in the aqueous ATRP of DMA,[9] in conjunction with copper(I) bromide as catalyst and 2,2-bipyridine (bpy) as ligand (see Table 1). For a monomer concentration of 50% (w/w) (entries 1−4), the results followed the expected trend: as the proportion of water was increased, the polymerization became less controlled. The polydispersities of the purified polymers ranged from 1.29 to 1.43 as the water content varied from 0% to 75%. Essentially full conversions could be achieved for these polymerizations within a few hours. In contrast, in pure methanol only a slow rate of polymerization was obtained, and an incomplete conversion (82%) was achieved. It is also noteworthy, and perhaps surprising, that polymerizations of DMA in alcoholic media do not appear to be better controlled than syntheses carried out in pure water. Indeed, in a control experiment the aqueous ATRP of 50% (w/w)

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Table 1. ATRP of DMA in Methanol or Methanol/Water Mixtures at Ambient Temperature[a]

entry	solvent (% w/w)	DMA (% w/w)	time (h)	conversion (%)	M_n^b (g/mol)	M_w/M_n^b	PMMA[c] (mol %)
1	MeOH	50	30.0	82	14 300	1.29	7
2	50:50 H_2O:MeOH	50	2.5	98	11 800	1.35	3
3	67:33 H_2O:MeOH	50	1.0	99	10 700	1.40	2
4	75:25 H_2O:MeOH	50	1.0	98	9 600	1.43	1
5	MeOH	67	18.0	99	13 700	1.50	2
6	MeOH	33	168.0	70	9 860	1.73	26

[a] For all entries, $[DMA]_0$:[MBP]:[CuBr]:[bpy] = 50:1:1:2. [b] Determined by GPC analysis in THF eluent and calibrated with poly(methyl methacrylate) standards. [c] MMA content (mol %) of the isolated DMA "homopolymer" , as calculated by ^{1}H NMR.

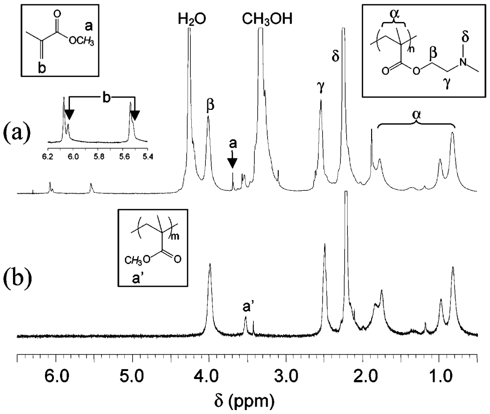


Figure 1. ^{1}H NMR spectra ($CDCl_3$) of the ATRP of 50% (w/w) DMA in methanol at 20 °C: (a) after 24 h; (b) after purification of the copolymer. $[DMA]_0$:[MBP]:[CuBr]:[bpy] = 50:1:1:2 (see entry 1 in Table 1).

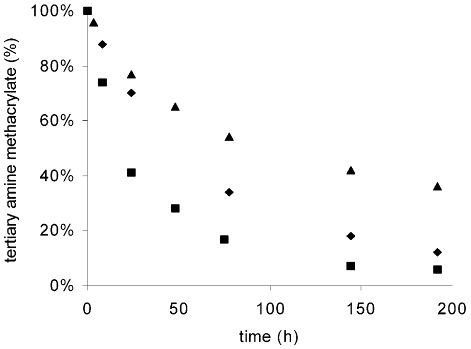


Figure 2. Kinetics of transesterification of DMA (◆), DEA (■), and DPA (●) in methanol at 20 °C. Conditions: 8.0 mmol of tertiary amine methacrylate, 48.0 mmol of methanol.

DMA led to 99% conversion within 30 min and yielded a final polydispersity of 1.24. For the homopolymerization of DMA in methanol, we noticed the appearance of new vinyl peaks in the ^{1}H NMR spectra recorded during kinetics studies (Figure 1a). These "ghost" vinyl peaks were also observed for all polymerizations conducted in methanol:water mixtures, but not for polymerizations conducted in pure water (see Table 1). At this stage, it was conceivable that the Cu(I) catalyst might promote transesterification. Thus, to determine whether these peaks were in some way due to the ATRP synthesis conditions, DMA and methanol were mixed in the same molar ratio as that used for a typical ATRP synthesis, in the absence of any catalyst or initiator, and ^{1}H NMR spectra were recorded in $CDCl_3$ at various time intervals. The same "ghost" vinyl signals were observed, and after comparison with various pure compounds, they were assigned to the vinyl signals of MMA. On closer inspection, additional NMR signals attributable to 2-(dimethylamino)ethanol were also observed.

The hydrolytic instability of DMA in water is well documented,[11] but its instability in methanol, and possibly other primary alcohols, is less well established. The rate of hydrolysis of DMA reported by Hennink and co-workers[11] is likely to be negligible for the aqueous ATRP of DMA since this polymerization is very fast at 20 °C.[8] In contrast, the relatively slow rate of ATRP of DMA in methanol is comparable to the rate of transesterification. For example, alcoholic ATRP of hydrophilic methacrylates at room temperature typically requires at least 5−8 h to achieve high conversions, while 15 mol % DMA was converted to methyl methacrylate via spontaneous transesterification at 20 °C within 24 h. Therefore, the ATRP of DMA in methanol is expected to lead to undesired *statistical copolymers* of DMA and methyl methacrylate. This problem was verified by inspecting the ^{1}H NMR spectrum of the purified polymer (see Figure 1b): a broad signal appeared at δ 3.6−3.7, corresponding to the three protons of the methoxy group of poly(methyl methacrylate). Thus, a statistical copolymer containing 7 mol % MMA residues was produced, rather than the target DMA homopolymer. When water was used as a cosolvent, the degree of transesterification was somewhat lower (1−3 mol %) due to the faster rate of ATRP (see entries 2−4 in Table 1). The ATRP of DMA in methanol was also carried out at different monomer concentrations. At 33% (w/w) DMA, the DMA−MMA statistical copolymer that was produced contained up to 26% MMA (entry 6). In contrast, at 66% (w/w) DMA only 2% MMA was incorporated due to the faster rate of polymerization at this higher monomer concentration. It is worth emphasizing that, in contrast to DMA monomer, DMA homopolymer does not undergo transesterification in methanol. Similar observations regarding the relative stabilities of DMA monomer and homopolymer toward hydrolysis were reported by Hennink and co-workers.[11]

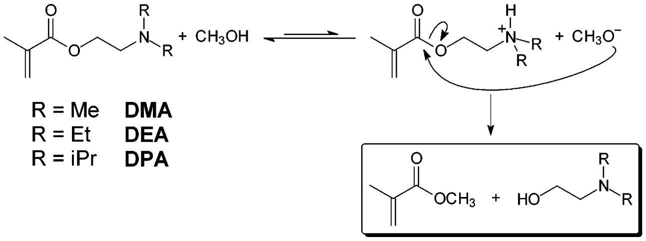
Transesterification has also been observed for two related tertiary amine methacrylates, namely 2-(diethylamino)ethyl methacrylate (DEA) and 2-(diisopropylamino)ethyl methacrylate (DPA). These monomers exhibited comparable reactivities toward methanol, affording MMA and the corresponding 2-(dialkylamino)ethanol. The kinetics of transesterification of equimolar solutions of DMA, DEA, and DPA in methanol at 20 °C are compared in Figure 2: the correlation between the extent of transesterification and the pK_b suggests that base catalysis is involved (see Table 2). Thus, the relative propensity of these tertiary amine methacrylates toward transesterification is DEA > DMA > DPA. Moreover, 2-(*N*-morpholino)ethyl methacrylate (MEMA), which is a rather weaker base (pK_b = 7.8), proved to be much less susceptible toward transesterification. (No change in the ^{1}H NMR spectrum of a MEMA/methanol mixture was observed after 8 days at 20 °C.) This observation is consistent with the fact that transesterification is also not observed for many other non-amine

Table 2. Relationship between the pK_b Values of DMA, DEA, DPA, and MEMA and Their Relative Rates of Transesterification

compound	pK_b[a]	$t_{1/2}$ (h)[b]
DMA	5.3	46
DEA	4.7	20
DPA	5.7	93
MEMA	7.8	

[a] pK_b = 14 − pK_a, where the pK_a was determined by titrating an aqueous solution of 0.1 M tertiary amine methacrylate (previously acidified with 0.1 M HCl) with 0.1 M NaOH. [b] Time at which 50 mol % of the tertiary amine methacrylate has been converted into MMA.

Scheme 1. Suggested Mechanism for the Self-Catalyzed Transesterification of Tertiary Amine Methacrylates with Methanol at Room Temperature



methacrylates such as 2-hydroxyethyl methacrylate (HEMA) or 2-methacryloyloxyethyl phosphorylcholine (MPC). Presumably, the basic tertiary amine groups lead to self-catalyzed transesterification (see Scheme 1). Similar transesterification experiments were conducted using 2-propanol (IPA) instead of methanol. None of the four tertiary amine methacrylates reacted with IPA because this secondary alcohol is more sterically congested and hence less prone to transesterification. In this context we note that McDonald and Rannard recently reported the controlled homopolymerization of *n*-butyl methacrylate in IPA/water mixtures.[14] These workers found that relatively small amounts (ca. 7% (v/v)) of added water had a profound effect on the rate of polymerization, without loss of living character.

In our earlier publications we described the synthesis of various DEA-based diblock copolymers using ATRP in methanol at elevated temperatures (50−60 °C).[12,13] We reexamined these studies in order to determine whether the DEA blocks were genuine homopolymers or were actually DEA/MMA statistical copolymers. Close inspection of the ^{1}H NMR spectra confirmed that no MMA was present in any of these diblock copolymers. This indicates that the rate of transesterification of DEA with methanol is negligible compared to the rate of polymerization of DEA when the ATRP synthesis is conducted at higher temperatures.

Conclusions

The unexpected propensity for tertiary amine methacrylates to undergo transesterification under mild conditions in methanol was observed for the first time. This side reaction indicates that methanol should not be used as a (co)solvent for the ATRP of DMA, DEA, or DPA at ambient temperature. Fortunately, several protocols are available for the synthesis of controlled-structure tertiary amine methacrylate copolymers in protic media. For example, transesterification of each of these monomers with IPA is extremely slow relative to the time scale of the polymerization. Thus, although the rate of ATRP is slower in IPA, this secondary alcohol can be a useful alternative solvent to methanol. Perhaps surprisingly, the presence of methanol can be tolerated if ATRP syntheses are carried out at higher temperatures (>50 °C). Finally, if it is desirable that the ATRP syntheses are conducted at room temperature, water can be added to accelerate the rate of polymerization in order to minimize the effect of transesterification.

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