Use of Ascorbic Acid as Reducing Agent for Synthesis of Well-Defined Polymers by ARGET ATRP

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Since its discovery in 1995, atom transfer radical polymerization (ATRP)[1,2] has become an efficient technique for synthesis of polymers with precisely controlled molecular architecture (topology, composition, functionality)[3−6] and for the preparation of various hybrid materials[7−16] and bioconjugates.[17−24] We have recently reported three new initiating systems based on activators generated by electron transfer (AGET),[25,26] activators regenerated by electron transfer (ARGET),[27−29] and initiators for continuous activator regeneration (ICAR).[29] These techniques employ oxidatively stable Cu(II) complexes that are activated in the presence of various reducing agents. In AGET, essentially all Cu(II) species are quickly reduced to a Cu(I) state, and a normal ATRP starts in the presence of >1000 ppm (>0.1 mol % vs monomer) catalyst. AGET has been successfully carried out in organic solvents, in water, and also in various dispersed media.[25,26,30−34] The requirements for the reduction process in an AGET system are very different from those in the recently developed ARGET and ICAR methods. The ARGET process uses a much lower concentration of catalyst and relies on a slow steady regeneration of Cu(I) from Cu(II) species that are continuously formed by unavoidable radical termination reactions (as illustrated in Scheme 1). Consequently, the amount of Cu(II) added to the reaction is much smaller than the amount of reducing agent needed to balance the termination process.

Various reducing agents have been reported for a successful AGET ATRP, including tin(II) 2-ethylhexanoate in organic media and ascorbic acid in aqueous systems. Ascorbic acid is a strong reducing agent, and it very quickly converts Cu(II) to Cu(I) species. Very fast reduction process of Cu(II) complexes by ascorbic acid diminishes their concentration to a very low level, increases concentration of radicals, and decreases polymerization control. This suggests that ascorbic acid should not be used for ARGET ATRP, in which the concentration of Cu(II) complexes is maintained by balancing a slow termination process with an equally slow and steady reduction process. Thus, phenols, glucose, hydrazine, Sn(II) species, and radical initiators (ICAR) were preferentially used for that purpose.[27−29]

Herein, we show that ascorbic acid can be successfully applied to ARGET, but under heterogeneous conditions, when its limited solubility in reaction medium allows a controlled ARGET ATRP.

Table 1 illustrates results of an ARGET ATRP of methyl acrylate (MA) in the presence of various amounts of $CuBr_2$/tris(2-(dimethylamino)ethyl)amine (Me_6TREN) complexes and ascorbic acid under homogeneous conditions (in *N*,*N*-dimethylformamide (DMF)) and under heterogeneous conditions (in anisole in which ascorbic acid has limited solubility[35]).

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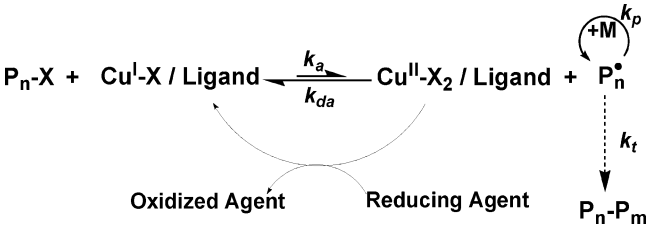
Scheme 1. Proposed Mechanism for ARGET ATRP



Polymerization in DMF initially proceeded faster than that in anisole and led to polymers with higher polydispersity. This is especially noticeable in the polymerization when 250 ppm of Cu was used: polymers were obtained with molecular weights much higher than expected, indicating limited initiation efficiency (∼41%). However, by changing the solvent to anisole, a significantly higher level of control was achieved. Figure 1 compares kinetics and evolution of molecular weights and polydispersities with conversion for two selected experiments. ARGET ATRP under heterogeneous conditions approached ∼80% MA conversion in less than 3 h. The experimental molecular weights, determined by GPC using polystyrene standards, were in good agreement with the theoretical values, indicating high initiation efficiency. The molecular weight distribution (MWD, M_w/M_n) remained 1.1−1.3 for the entire polymerization, indicating that control was quickly attained and retained.

The concentration of Cu was further decreased to a lower level, e.g., 25 ppm, when anisole was used as solvent. When the reaction was carried out in DMF (Table 1, entry 3) the polymerization was still poorly controlled, evidenced by the relatively broad MWD ($M_w/M_n = 1.6$). In contrast, the polymerization conducted in anisole (Table 1, entry 4) was well-controlled. The monomer conversion increased to over 90% after 5 h, experimental molecular weights were in good agreement with the theoretical values, and the GPC traces symmetrically shifted to higher molecular weight, indicating high initiation efficiency.

It was further observed that a higher amount of reducing agent, ascorbic acid, resulted in a higher polymerization rate, as illustrated in Figure 2. When the amount of reducing agent was 100 times higher than that of the Cu(II) catalyst (200 times higher than the stoichiometrical amount), the polymerization reached over 90% MA conversion in ∼3 h. The higher polymerization rate indicates that, in addition to a homogeneous reaction with sparingly soluble ascorbic acid, some contribution of the heterogeneous redox reaction between the Cu(II) catalysts and the surface of the solid ascorbic acid may also occur.

ARGET ATRP was also attempted with only 10 ppm of Cu (Table 1, entry 6). The polymerization reached ∼90% conversion in 5 h. This polymerization displayed moderate control, as evidenced by a constant radical concentration and the relatively narrow MWD of the obtained polymers. All polymerizations carried out with 25 ppm or lower concentration of Cu resulted in the preparation of essentially colorless polymers; therefore, catalyst removal may not be necessary for some applications.

ARGET ATRP of *n*-butyl acrylate (BA), methyl methacrylate (MMA), and styrene (St) with the aid of heterogeneous redox reactions was also successful, as illustrated in Table 1, entries 7−9. With 25 ppm of Cu, polymers with polydispersity below 1.3 were prepared. For St, the polymerization temperature was 90 °C in order to obtain an appropriate polymerization rate.

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Table 1. Synthesis of PolyMA, PolyBA, PolyMMA, and PolySt by ARGET ATRP Using Ascorbic Acid as Reducing Agent[a]

entry	monomer	ascorbic acid (to Cu, in mol)	Cu (ppm)[b]	solvent	time (h)	conv (%)	M_n(theo)	M_n(GPC)	M_w/M_n
1[c]	MA	10	250	DMF	1.5	74	25 460	62 550	1.52
2[c]	MA	10	250	anisole	2.2	87	30 000	28 000	1.14
3[d]	MA	10	25	DMF	1.5	76	26 100	32 700	1.60
4[d]	MA	10	25	anisole	5.3	87	30 000	27 700	1.19
					17	98	33 750	34 000	1.18
5[d]	MA	100	25	anisole	3.3	93	32 020	34 400	1.30
6[e]	MA	10	10	anisole	6	91	31 340	29 700	1.40
7[d]	BA	10	25	anisole	21.5	89	45 500	43 000	1.28
8[d]	MMA	10	25	anisole	18	59	23 260	30 700	1.27
9[d]	St	10	25	anisole	64.7	68	27 580	25 200	1.18
10[f]	St	10	25	anisole	52	55	53 540	60 900	1.27

[a] Polymerizations were carried out in 60% solutions of monomer (in volume). Initiator: ethyl 2-bromoisobutyrate (EBiB) for MA, BA, and St; ethyl α-bromophenylacetate for MMA. Ligand: Me_6TREN. The amount of ligand has been fixed at 10 times the amount of Cu(II) initially added to the reaction in order to ensure coordination of the ligand with Cu(II) in the presence of a large excess of monomer.[27−29] Polymerization temperatures: 60 °C for MA, BA, and MMA; 90 °C for St. [b] Concentration of Cu: molar ratio of Cu to monomer. [c] [M]:[I]:[Cu(II)] = 400:1:0.1. [d] [M]:[I]:[Cu(II)] = 400:1:0.01. [e] [M]:[I]:[Cu(II)] = 400:1:0.004. [f] [St]:[PMA-Br]:[Cu(II)] = 400:1:0.01.

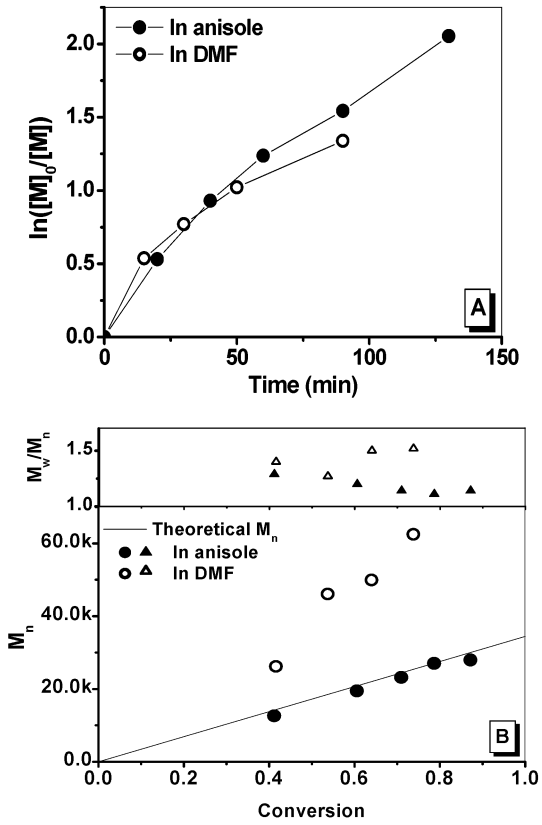

Figure 1. (A) First-order kinetic plot and (B) molecular weight evolution with conversion in ARGET ATRP of MA with ascorbic acid as reducing agent in anisole and DMF. Polymerization conditions: Table 1, entries 1 and 2.

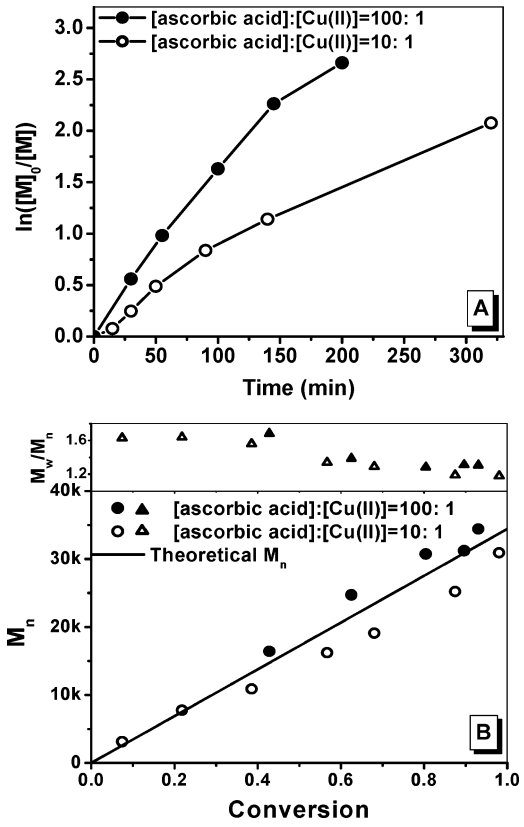

Figure 2. (A) First-order kinetic plot and (B) molecular weight evolution with conversion in ARGET ATRP of MA with various amounts of ascorbic acid as reducing agent in anisole. Polymerization conditions: Table 1, entries 4 and 5.

In order to evaluate the livingness of the polymerization, i.e., the retention of active chain-end functionality in the polymers, the macroinitiator prepared in entry 4 of Table 1 (reaction was stopped at 98% conversion) was chain extended with St (Table 1, entry 10). High functionality was proved by the successful block copolymerization. The GPC traces of the block copolymer symmetrically shifted toward the higher molecular weight, indicating high cross-propagation efficiency.

Recently, Cu(0) was applied as a heterogeneous reducing agent for ATRP of methyl acrylate and vinyl chloride.[36] Although another mechanistic explanation was proposed (outer-sphere electron transfer between Cu(0) and dormant species), it is possible that Cu(0) acts as a reducing agent which slowly reduces Cu(II) species under heterogeneous conditions in ARGET ATRP, just as ascorbic acid does in the presently reported heterogeneous system.

In conclusion, a heterogeneous redox reaction between ascorbic acid, sparingly soluble in anisole, and Cu(II) species is sufficiently slow to maintain a slow but efficient regeneration of Cu(I) species. This results in well-controlled ARGET ATRP of methyl acrylate, *n*-butyl acrylate, methyl methacrylate, and styrene. The use of ascorbic acid as an environmentally friendly reducing agent provides a safe and controlled ATRP procedure for the production of commercially viable functional/responsive polymers with unnecessary, or reduced, catalyst removal costs.

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Supporting Information Available: Procedures of ARGET ATRP under homogeneous and heterogeneous redox reactions and the relative kinetic plots that are not included in the main text. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wang, J.-S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614−5615.
(2) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721−1723.
(3) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921−2990.
(4) Gao, H.; Tsarevsky, N. V.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 5995−6004.
(5) Davis, K. A.; Matyjaszewski, K. *Adv. Polym. Sci.* **2002**, *159*, 1−166.
(6) Coessens, V.; Pintauer, T.; Matyjaszewski, K. *Prog. Polym. Sci.* **2001**, *26*, 337−377.
(7) Edmondson, S.; Osborne, V. L.; Huck, W. T. S. *Chem. Soc. Rev.* **2004**, *33*, 14−22.
(8) Pyun, J.; Kowalewski, T.; Matyjaszewski, K. *Macromol. Rapid Commun.* **2003**, *24*, 1043−1059.
(9) von Werne, T.; Patten, T. E. *J. Am. Chem. Soc.* **2001**, *123*, 7497−7505.
(10) Yu, W. H.; Kang, E. T.; Neoh, K. G.; Zhu, S. *J. Phys. Chem. B* **2003**, *107*, 10198−10205.
(11) Kong, H.; Gao, C.; Yan, D. *J. Am. Chem. Soc.* **2004**, *126*, 412−413.
(12) Becker, M. L.; Liu, J.; Wooley, K. L. *Biomacromolecules* **2005**, *6*, 220−228.
(13) Ohno, K.; Morinaga, T.; Koh, K.; Tsujii, Y.; Fukuda, T. *Macromolecules* **2005**, *38*, 2137−2142.
(14) Cai, Q. J.; Fu, G. D.; Zhu, F. R.; Kang, E.-T.; Neoh, K.-G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1104−1107.
(15) Li, D.; Jones, G. L.; Dunlap, J. R.; Hua, F.; Zhao, B. *Langmuir* **2006**, *22*, 3344−3351.
(16) Azzaroni, O.; Brown, A. A.; Huck, W. T. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1770−1774.
(17) Licciardi, M.; Tang, Y.; Billingham, N. C.; Armes, S. P.; Lewis, A. L. *Biomacromolecules* **2005**, *6*, 1085−1096.
(18) Bontempo, D.; Heredia, K. L.; Fish, B. A.; Maynard, H. D. *J. Am. Chem. Soc.* **2004**, *126*, 15372−15373.
(19) Mei, Y.; Beers, K. L.; Byrd, H. C. M.; VanderHart, D. L.; Washburn, N. R. *J. Am. Chem. Soc.* **2004**, *126*, 3472−3476.
(20) Tao, L.; Mantovani, G.; Lecolley, F.; Haddleton, D. M. *J. Am. Chem. Soc.* **2004**, *126*, 13220−13221.
(21) Bontempo, D.; Li Ronald, C.; Ly, T.; Brubaker, C. E.; Maynard, H. D. *Chem. Commun.* **2005**, 4702−4704.
(22) Heredia, K. L.; Bontempo, D.; Ly, T.; Byers, J. T.; Halstenberg, S.; Maynard, H. D. *J. Am. Chem. Soc.* **2005**, *127*, 16955−16960.
(23) Sen Gupta, S.; Raja, K. S.; Kaltgrad, E.; Strable, E.; Finn, M. G. *Chem. Commun.* **2005**, 4315−4317.
(24) Chen, G.; Huynh, D.; Felgner, P. L.; Guan, Z. *J. Am. Chem. Soc.* **2006**, *128*, 4298−4302.
(25) Min, K.; Gao, H.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2005**, *127*, 3825−3830.
(26) Jakubowski, W.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 4139−4146.
(27) Jakubowski, W.; Min, K.; Matyjaszewski, K. *Macromolecules* **2006**, *39*, 39−45.
(28) Jakubowski, W.; Matyjaszewski, K. *Angew. Chem.* **2006**, *118*, 4594−4598.
(29) Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, W.; Huang, J.; Braunecker, W. A.; Tsarevsky, N. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15309−15314.
(30) Min, K.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 8131−8134.
(31) Hizal, G.; Tunca, U.; Aras, S.; Mert, H. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 77−87.
(32) Min, K.; Jakubowski, W.; Matyjaszewski, K. *Macromol. Rapid Commun.* **2006**, *27*, 594−598.
(33) Min, K.; Gao, H.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2006**, *128*, 10521−10526.
(34) Oh, J. K.; Tang, C.; Gao, H.; Tsarevsky, N. V.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2006**, *128*, 5578−5584.
(35) A precise solubility of ascorbic acid in the reaction mixture is difficult to determine because the solubility is extremely low, and it varies with temperature, monomer concentration, and monomer conversion during polymerization. The solubility of ascorbic acid in anisole was qualitatively evaluated by mixing 5 mg of ascorbic acid and 500 mL of anisole. After stirring the mixture for 24 hours at RT, the insoluble solid ascorbic acid powder was clearly observed. Based on the observation, the solubility of ascorbic acid in anisole at RT should be lower than 1.0 mg/100 mL.
(36) Percec, V.; Guliashvili, T.; Ladislaw, J. S.; Wistrand, A.; Stjerndahl, A.; Sienkowska, M. J.; Monteiro, M. J.; Sahoo, S. *J. Am. Chem. Soc.* **2006**, *128*, 14156−14165.

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