Synthesis of amino acid-based polymers *via* atom transfer radical polymerization in aqueous media at ambient temperature†

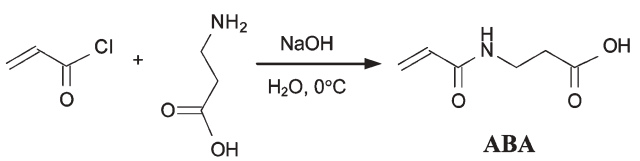
Il-Doo Chung,[a] Philip Britt,[b] Dong Xie,[c] Eva Harth[d] and Jimmy Mays*[ab]

Received (in Columbia, MO, USA) 29th October 2004, Accepted 23rd November 2004
First published as an Advance Article on the web 10th January 2005
DOI: 10.1039/b416591h

Well-defined acryloyl β-alanine (ABA) polymers were synthesized directly *via* atom transfer radical polymerization (ATRP) under near physiological conditions using various water soluble initiators with high yield and narrow molecular weight distributions.

Among the techniques that allow the synthesis of well-defined homopolymers and copolymers, atom transfer radical polymerization (ATRP) is one of the most useful systems, due to its tolerance of impurities, the ready availability of many kinds of initiators, catalysts and monomers, its mild reaction conditions, and its ability to produce polymers with predetermined molecular weights and narrow polydispersities.[1–3] We previously reported a number of studies on the synthesis and properties of polymers based on monomers derived from the reaction of amino acids with acryloyl or methacryloyl chloride.[4–8] Although ATRP has been applied to a wide variety of functional monomers, to the best of our knowledge there has been only one report in the literature addressing ATRP of amino acid-based monomers.[9] However, in practice, the methodology used in this prior work has some disadvantages such as use of DMSO as solvent and other toxic organic solvents for purification, water insolubility of the resulting polymers, and a somewhat higher polymerization temperature. An alternative and more practical way to synthesize well-defined acidic polymers is the direct polymerization of acidic monomers in their sodium salt form by ATRP in protic media.[10,11] Although a third approach, protecting and deprotecting acidic functionalities with *tert*-butyl groups, is also feasible, multistep syntheses and slow polymerization rates due to the steric hindrance of bulky monomers are major factors in the failure for practical use.[12–15]

This communication describes the successful polymerization of acryloyl β-alanine (ABA) *via* ATRP in water and water–methanol mixtures at ambient temperature. (Scheme 1—see ESI† for a detailed experimental protocol for the synthesis of ABA).



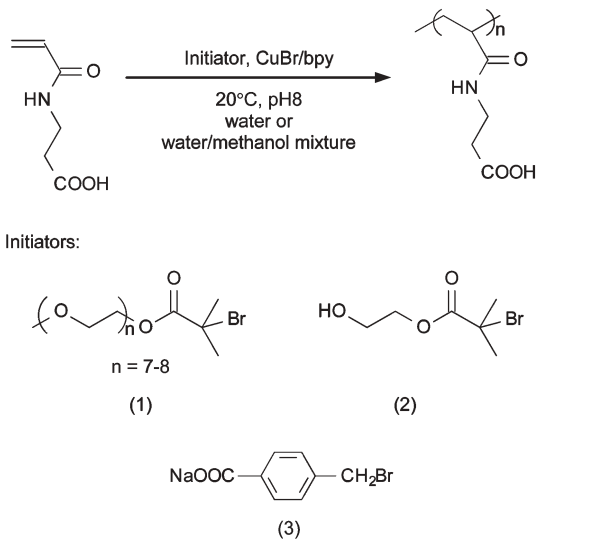
Scheme 1 Synthesis of ABA from β-alanine.

† Electronic supplementary information (ESI) available: experimental protocol and spectroscopic characterization. See http://www.rsc.org/suppdata/cc/b4/b416591h/

*jimmymays@utk.edu

Controlled polymerization of amino acid-based monomers is important as a tool for synthesis of tailored polymers and copolymers for biomaterials and medical applications. Such amino acid-based polymers are expected to be non-toxic, since a wide variety of polymers having amino acid moieties either in the main chains or in side chains, such as poly(glutamic acid) and polyleucine, have been synthesized, and they exhibited biocompatibility and biodegradability similar to polypeptides.[16]

ATRP of ABA using **1**, **2** and **3** as initiators in conjunction with CuBr and 2,2′-bypyridine (bpy) was carried out in aqueous solution at ambient temperature. The water soluble initiators were synthesized by the reaction of 2-bromoisobutyryl bromide with monomethoxy-capped poly(ethylene glycol)[10] or ethylene glycol.[17] A typical ATRP of ABA was carried out in doubly distilled, deionized water at ambient temperature under a nitrogen atmosphere (Scheme 2). ABA was dissolved in deionized water with the addition of NaOH (pH 8), and added to a Schlenk flask with magnetic stir bar, and the reagent mixture was degassed by three freeze–pump–thaw cycles. The flask was back-filled with nitrogen, and the CuBr catalyst, and bpy ligand were quickly added to the stirred solution under nitrogen. An aqueous degassed solution of initiator at pH 8 was added to this reaction solution to start polymerization. The reaction solution immediately became dark brown and more viscous with exotherms of 7–9 °C.



Scheme 2 Atom transfer radical polymerization of ABA in aqueous media at 20 °C with various initiators.

Table 1 Summary of conversion, molecular weight and polydispersity data for homopolymerization of ABA using various initiators in protic media at 20 °C[a]

Initiator type	Solvent H_2O : MeOH	Time/h	Conversion (%)[b]	Molecular weight			
				M_n(theory)[c]	M_n(GPC)[d]	M_n(exp)	M_w/M_n[d]
1	100 : 0	4	97	8260	13 300	7900[e]	1.16
1	100 : 0	4	92	11 540	—	8990[e]	—
1	60 : 40	18	95	11 900	9880	17 800[d,f]	1.22
2	60 : 40	6	90	7500	9970	12 300[d,f]	1.22
2	60 : 40	6	92	11 300	12 300	15 900[d,f]	1.21
2	60 : 40	18	92	11 300	12 500	15 900[d,f]	1.20
3	100 : 0	4	97	7980	11 700	10 000[b]	1.16
3	60 : 40	18	93	7660	11 600	9230[b]	1.13
3	60 : 40	18	82	10 100	10 200	11 700[b]	1.25

[a] Synthesis conditions: [ABA] = 1.747 M. The molar ratio of initiator : CuBr : bpy was 2 : 2 : 5 in all experiments. [b] Determined from ^{1}H NMR. [c] Calculated from the following equation: M_n(theory) = 143.1([ABA]$_0$/[initator]) × %Conversion/100 + M_w(initiator). [d] Determined by GPC analysis [THF containing 0.25 wt% tetrabutylammonium bromide, PSt standards, RI, UV, TALS (two angle light scattering) detectors] after PABA was converted into its methyl ester form. PABA homopolymer was treated with diazomethane, which was generated from diazald reacted with KOH in water–ethanol solution at 65 °C, to obtain partially esterified products, having solubility in THF for M_w determination (see ref. 18). [e] M_w determined from the multi-angle light scattering (MALS) detector in water at 20 °C. [f] Determined from TALS (15° and 90°) detector with a 680 nm laser and a refractive index detector.

To terminate the polymerization, the dark brown solution was bubbled with oxygen gas, diluted with water, and acidified with a solution of concentrated HCl (37%). The spent ATRP catalyst was removed by treatment with silica gel, followed by dialysis against deionized water for 48 h with periodic bath changes to remove unreacted monomers. The dialysis products were freeze-dried.

The monomer consumption was monitored by ^{1}H NMR spectroscopy as a function of time. The signal from methine protons of the polymer backbone at 1–2 ppm increased gradually, together with the reduction of the vinyl peaks at 6.09 and 5.62 ppm, which were ascribed to the ABA monomer (see ESI†). Like the ATRP of other hydrophilic monomers reported elsewhere,[10] high conversions were achieved in short times in protic media at 20 °C for the ATRP of ABA, which means that the rate of polymerization is extremely fast under remarkably mild conditions.

^{1}H NMR spectroscopy was also used to determine the number average molecular weight of the purified PABA prepared using initiator **3** by comparing the intensity of the aromatic protons at 7.8 and 7.2 ppm of the initiator with that due to the methylene protons of the PABA residues at 2.5 ppm. Good agreement of M_n(NMR) and M_n(theory) shows that the molecular weight of PABA could be controlled by the monomer : initiator molar ratio, which is supporting evidence for a living polymerization (see ESI† and Table 1). The molecular weights of the polymers increased with conversion, as expected for a living polymerization, but the plots were not strictly linear. This supports the earlier report by Armes *et al.* that the kinetics for ATRP of acidic monomers is complex.[11] It was impossible to determine M_n of polymers prepared using initiators **1** and **2** by NMR calculations due to the overlapping peaks of initiator and PABA residues. Table 1 summarizes molecular weights, polydispersities, and conversion data for homopolymers. GPC analysis indicates that the homopolymerization of ABA using the three different initiators afforded relatively narrow, monomodal peaks with polydispersities of around 1.13 to 1.25 and proceeded to high conversions (>90%) in either water or a 60 : 40 water–methanol mixture (ESI and Table 1). Some deviations between the molecular weights determined by GPC and theoretical M_n were found, which may be due to the difference in the hydrodynamic volumes of the polystyrene standard and the resulting polymers.

Static light scattering from some polymers was also measured to obtain weight average molecular weights. The specific refractive index increments (dn/dc) of PABA in water at 20 °C and in THF at 40 °C were determined using a refractive index detector (Wyatt OPTILAB DSP). A detailed experimental protocol is available as Supporting Information.† The measured dn/dc values at 690 nm were 0.1572 ml g^{-1} in water for PABA and 0.101 ml g^{-1} in THF for methylated PABA. The molecular weights of PABA obtained by this method, especially by MALS, are in good agreement with the theoretical molecular weights (see Table 1).

In summary, well-defined, potentially biocompatible natural amino acid-based polymers, PABA, were synthesized by ATRP in aqueous media under conditions very close to physiological conditions, potentially facilitating functionalization of proteins or biomaterials that cannot be functionalized in organic solvents. High monomer conversions under mild conditions (20 °C) and narrow polydispersities of the resulting PABA are clear indications of a controlled polymerization mechanism. All three of the initiator systems used afforded good results, but the ethylene glycol-based initiator may be preferred over the other initiators based on biocompatibility considerations. Future studies will focus on the use of ATRP to synthesize amino acid-based di- and tri-block amphiphilic copolymers, which may have use in biotechnology applications by fabricating self-assembled biocompatible micelles for hydrophobic drug delivery. We will also explore polymerization of other amino acids in order to determine how general this procedure is for producing well-defined amino acid-based polymers.

Research sponsored by the ORNL Laboratory Director's Research and Development Program, US Department of Energy, under contract No. DE-AC05-00OR22725 with Oak Ridge National Laboratory, managed and operated by UT-Battelle, LLC.

Il-Doo Chung,[a] Philip Britt,[b] Dong Xie,[c] Eva Harth[d] and Jimmy Mays*[ab]
[a]*Department of Chemistry, University of Tennessee, Knoxville, TN 37996, USA. E-mail: jimmymays@utk.edu; Fax: +1 865 974 9304; Tel: +1 865 974 0747*
[b]*Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA. E-mail: brittpf@ornl.gov; Fax: +1 865 576 7956; Tel: +1 865 574 5029*
[c]*Department of Biomedical Engineering, Indiana University Purdue University Indianapolis, Indianapolis, IN 46202, USA. E-mail: dxie@iupui.edu; Fax: +1 317 278 2032; Tel: +1 317 274 9748*
[d]*Department of Chemistry, Vanderbilt University, Nashville, TN 37235, USA. E-mail: eva.harth@vanderbilt.edu; Fax: +1 615 343 3405; Tel: +1 615 343 3405*

Notes and references

1 J. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614.
2 M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721.
3 K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921.
4 D. Xie, I. Chung, W. Wu, J. Lemons, A. Puckett and J. Mays, *Biomaterials*, 2004, **25**, 1825.
5 D. Xie, I. Chung, W. Wu and J. Mays, *Dent. Mater.*, 2004, **20**, 470.
6 D. Xie, W. Wu, A. Puckett, B. Farmer and J. Mays, *Eur. Polym. J.*, 2004, **40**, 343.
7 W. Wu, D. Xie, A. Puckett and J. Mays, *Eur. Polym. J.*, 2003, **39**, 959.
8 D. Xie, D. Feng, I. Chung and A. W. Eberhardt, *Biomaterials*, 2003, **24**, 2749.
9 L. Ayres, M. R. J. Vos, P. J. H. M. Adams, I. O. Shklyarevskiy and J. C. M. Hest, *Macromolecules*, 2003, **36**, 5967.
10 E. J. Ashford, V. Naldi, R. O'Dell, N. C. Billingham and S. P. Armes, *Chem. Commun.*, 1999, 1285.
11 X. S. Wang, R. A. Jackson and S. P. Armes, *Macromolecules*, 2000, **33**, 255.
12 T. E. Patten and K. Matyjaszewski, *Adv. Mater.*, 1998, **10**, 901.
13 Q. Ma and K. L. Wooley, *J. Polym. Sci.: Part A: Polym. Chem.*, 2000, **38**, 4805.
14 K. A. Davis, B. Charleux and K. Matyjaszewski, *J. Polym. Sci.: Part A: Polym. Chem.*, 2000, **38**, 2274.
15 D. M. Haddleton, M. C. Crossman, B. H. Dana, D. J. Duncalf, A. M. Heming, D. Kukulj and A. J. Shooter, *Macromolecules*, 1999, **32**, 2110.
16 F. Sanda and T. Endo, *Macromol. Chem. Phys.*, 1999, **200**, 2651.
17 Z. Yin, C. Koulic, C. Pagnoulle and R. Jerome, *Macromolecules*, 2001, **34**, 5132.
18 M. Hudlicky, *J. Org. Chem.*, 1980, **45**, 5377.

