Highly Enantioselective Desymmetrization of Anhydrides by Carbon Nucleophiles: Reactions of Grignard Reagents in the Presence of (<M->)-Sparteine

Ryo Shintani and Gregory^^C. Fu*

Experimental Section

4-Vinylbenzoyl chloride was prepared from 4-vinylbenzoic acid [VBA] using thionyl chloride. The VBA starting material was synthesized from 4-(bromomethyl)benzoic acid using Wittig chemistry (L. M. Harwood, C. J. Moody, *Experimental Organic Chemistry, principles and practise*, Blackwell Scientific Pub, 588, **1989**). *t*-Butyl 4-vinylbenzoate [*t*-BuVBA] was synthesized by reacting 4-vinylbenzoyl chloride with excess *t*-butyl alcohol in dry diethyl ether in the presence of potassium *tert*-butoxide(T. Ishizone, A. Hirao, S. Nakahama, *Macromolecules* **1989**, *22*, 2895).
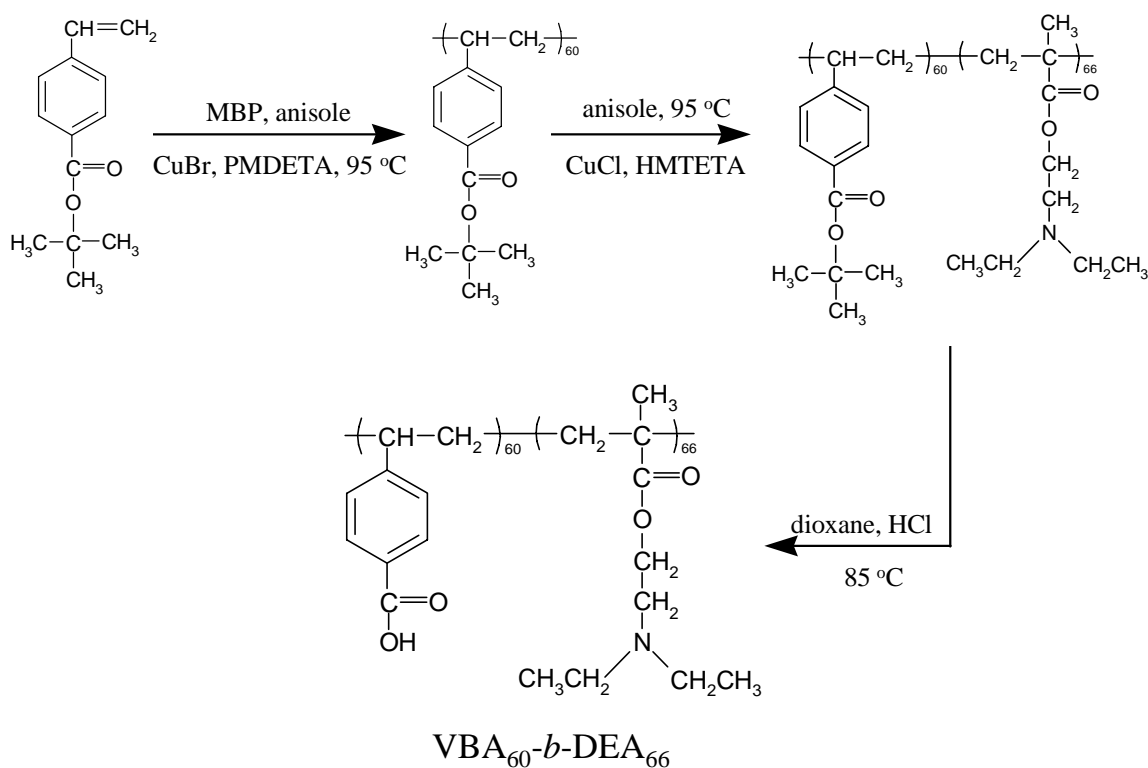
Scheme 1. The ATRP synthesis of the poly[4-vinylbenzoic acid-*block*-2-(diethylamino)ethyl methacrylate] (VBA—*b*-DEA) diblock copolymer.

(Scheme 1) For a typical ATRP snnthesis of the poly(*tert*-butyl 4-vinylbenzoate) macro-initiator, CuBr (143 mg, 1 mmol) were added to a dry, round-bottom flask equipped with a stir bar. After sealing it with a rubber septum, the flask was degassed and back-filled with nitrogen three times and then left under nitrogen. Anisole (8 mL) and *tert*-butyl 4-vinylbenzoate (15.0 g, 74 mmol) were added, both of which were deoxygenated and added via syringe that had been purged with nitrogen. The tridentate pentamethyldiethylenetriamine (PMDETA) ligand (173 mg, 1 mmol) was added to form the copper complex. Methyl 2-bromopropionate (MBrP) (167 mg, 1.00 mmol) was added to the flask and the flask was placed in a thermostated oil bath at 95 °C; after 3 h, the flask was cooled and dissolved in

dichloromethane. ^{1}H-NMR analysis indicated a monomer conversion of 67%. The polymer was purified by passing through an alumina column and after evaporating most of the solvent, it was precipitated into methanol. The polymer was then dried under vacuum at room temperature. GPC analysis (PMMA standards, THF eluent, refractive index detector) showed that this t-BuVBA macro-initiator had a number-average molecular weight (M_n) = 12,300 and an M_w/M_n of 1.09.

2-(Diethylamino)ethyl methacrylate [DEA] was polymerized using the t-BuVBA macro-initiator in anisole at 95 $^{\circ}$C. Up to 80 % conversion was obtained after two hours and the resulting crude t-BuVBA-b-DEA diblock copolymer was purified by passing the reaction solution through a neutral alumina column; the solvent and excess monomer was removed under vacuum. The degree of polymerization of the DEA block was determined to be 66 by ^{1}H NMR spectroscopy (see Figure 2), indicating a mean block composition of 52 mol% DEA. GPC analysis of this diblock copolymer gave a M_n of 21,400 and an M_w/M_n of 1.28, which is typical of copolymers prepared by ATRP. Selective hydrolysis of the t-butyl groups was readily achieved by refluxing the diblock copolymer in a 10 v/v% HCl/dioxane solution for 10 h at 85 $^{\circ}$C. The solution mixture was precipitated into acetone to isolate the resulting zwitterionic VBA-b-DEA diblock copolymer. Further purification was achieved by dissolution in water at pH 10, followed by adjusting the solution to neutral pH in order to precipitate the diblock copolymer around its isoelectric point. This precipitate was further purified by washing with acetone and then dried under vacuum at 50 $^{\circ}$C overnight.

Dynamic light scattering (DLS) studies were performed on a Brookhaven Instruments Corp. BI-200SM goniometer equipped with a BI-9000AT digital correlator using a solid-state laser (125 mW, λ = 532 nm) at a fixed scattering angle of 90°. The hydrodynamic diameter, D_h, and polydispersity of the micelles were obtained by a cumulants analysis of the experimental correlation function.

Static light scattering was performed using a *DAWN DSP* Laser Photometer, equipped with a 5 mW He-Ne laser (λ = 632.8 nm) and eighteen photodiode detectors at scattering angles ranging from 22.5° to 147°. M_w and R_g data were obtained using standard Zimm plot analyses. The *dn/dc* values of copolymer solutions comprising DEA-core micelles at pH 10 and VBA-core micelles at pH 2 were measured at 20 $^{\circ}$C using an Optilab DSP Interferometric refractometer (λ = 633.0 nm).

Electrophoresis measurements were carried out using a Malvern ZetaMasterS instrument. Zeta potentials were calculated from mobilities using the Henry equation and determined as a function of solution pH (0.02 M NaCl; 25 $^{\circ}$C).

Steady-state fluorescence measurements were carried out with a Cary Eclipse fluorescence spectrophotometer (VARIAN) at room temperature. Pyrene was used as a probe of the hydrophobic domains. The excitation wavelength (λ_{ex}) was 333 nm.

^{1}H NMR spectra were recorded on 10.0 g L^{-1} copolymer solutions in D_2O using a Bruker Avance DPX 300 MHz

spectrometer. TEM pictures were recorded on a Hitachi 7100 microscope. Samples were prepared by dipping a Formvar-coated copper grid into 0.50 g L^{-1} aqueous copolymer solution and RuO_4 vapor was used as a staining agent to enhance the contrast.

Surface tension (γ) measurements were carried out using a Krüss K10 tensiometer operating at 20 ^{o}C. Reproducibility was checked by frequent determination of the surface tension of de-ionized doubly-distilled water (72-73 mN m^{-1}).

The effect of copolymer concentration on micelle dimensions

It is also interesting to note that the aqueous solution behavior of this schizophrenic diblock copolymer also depends on its concentration. For a 10.0 g L^{-1} copolymer solution, DEA-core micelles of 35 nm diameter are formed at pH 10. On addition of HCl, relatively large colloidal aggregates of 122 nm are formed at pH 2; these supramolecular structures are much larger than the well-defined micelles obtained from a 1.0 g L^{-1} copolymer solution (see above). This difference can be attributed to the phase inversion that occurs on shifting from high pH to low pH. During micelle formation, there is competition between inter-chain aggregation and intra-chain collapse, the former leads to larger micelles and the latter leads to smaller micelles. At higher copolymer concentration, it is more likely that inter-chain aggregation dominates over intra-chain collapse, leading to the formation of larger micelles.
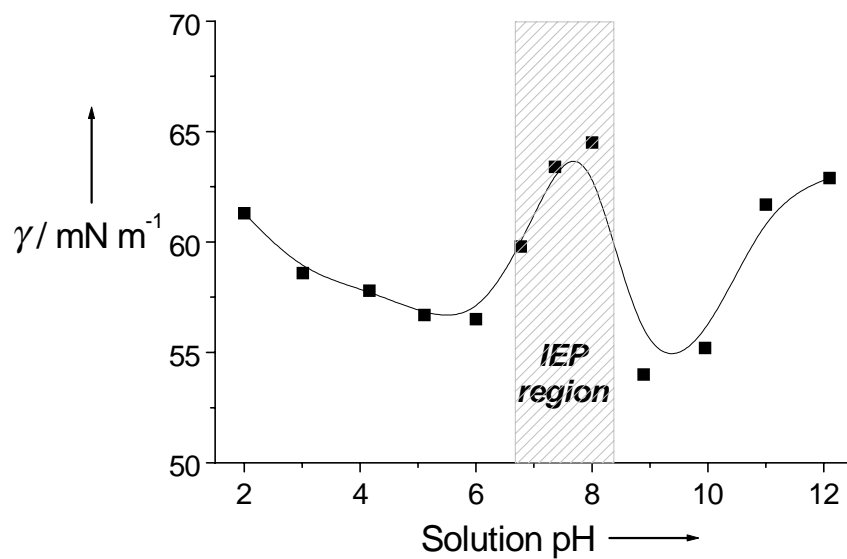
Surface tension studies

Figure 5a depicts the variation of surface tension with solution pH. As expected, the surface tension exhibited a maximum at around pH 7-8 due to macroscopic precipitation of the zwitterionic diblock copolymer. Above pH 8.3 or below pH 6.6, the surface tension decreased by about 7-10 mN m^{-1} due to weak interfacial adsorption. This moderate reduction in surface tension is perfectly reasonable given the polyelectrolyte nature of the hydrophilic block (anionic VBA or cationic DEA) at both high and low pH, respectively. The packing efficiency for the adsorbed chains at the air-water interface will be gradually reduced as the charge density of the cationic DEA (or anionic VBA) chains increases to its maximum value at pH 2 (or pH 10). This leads to the local minima observed in the surface tension data shown in Figure 5a.

Fluorescence studies

Pyrene has been used to probe the internal structure of the core of the micelles. The emission spectrum of pyrene depends on the hydrophobicity of the environment(A. S. Lee, A. P. Gast, V. Bütün, S. P. Armes, *Macromolecules* **1999**, *32*, 4302). Figure 5b shows the fluorescence intensity ratio (I_3/I_1) for pyrene in aqueous solutions of the VBA$_{60}$-b-DEA$_{66}$ diblock copolymer at different pH. The curve shows a minimum around the precipitation region; here the I_3/I_1 ratio is about 0.54, which is close to the literature value of pyrene in water, indicating that almost all the diblock copolymer chains precipitate at the IEP. At lower pH, a plateau at an I_3/I_1 ratio of about 0.65 was obtained, which

is lower than that expected for pyrene in a purely hydrophobic environment. This can be attributed to the relatively polar carboxylic acid groups in the VBA-core micelles or the low concentration (0.50 g L^{-1}) used in the fluorescence measurements. At higher pH, a relatively high I_3/I_1 ratio of about 0.82 was obtained, which corresponds to the formation of less polar DEA-core micelles.

Figure 5a. The variation of surface tension as a function of pH for a 1.0 g L^{-1} aqueous solution of the VBA_{60}–b-DEA_{66} zwitterionic diblock copolymer at 20 $^{\circ}C$.
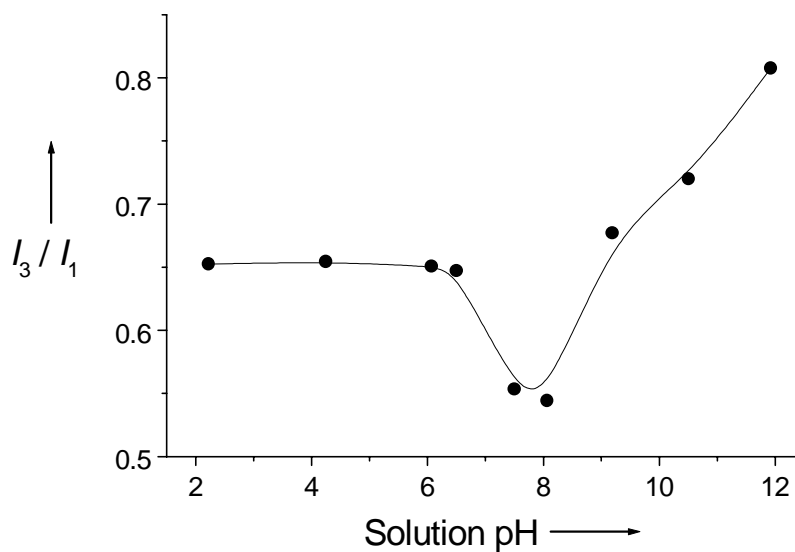
Figure 5b. I_3/I_1 intensity ratios derived from fluorescence emission spectra of a dilute solution (0.50 g L^{-1}) of the VBA_{60}-b-DEA_{66} diblock copolymer as a function of solution pH.