Catalytic Transfer Hydrogenation of Bifunctional Poly(ethylene glycol) Derivatives Using Palladium−Poly(ethylenimine) Catalyst

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Introduction

Synthesis of heterobifunctional derivatives (X-PEG-Y) and especially the purification of these products are somewhat difficult to accomplish. In fact, despite its relevance in biotechnology, only a few approaches have been reported in the literature.[1−3] The key and limiting step in the development of bifunctional derivatives is the ability to synthesize and purify monoprotected functionalized polymers. Different strategies are being studied in our laboratory in order to improve the methods to produce several bifunctional derivatives. One of these strategies includes the cleavage of the Z protecting group from Boc-PEG-Z derivatives by catalytic transfer hydrogenation with palladium black as a catalyst.[1] Once the Z group is removed, a functional amino group of the form Boc-PEG-NH_2 is obtained. However this approach provides a slow rate of the amino group deblocking and low yields. In this report, palladium−poly(ethylenimine) has been tested as an alternative catalyst. Poly(ethylenimine) has good mechanical and chemical stability and has been used as a support for metals.[4−6] Palladium−poly(ethylenimine) exhibits high catalytic activity and stability in the hydrogenolysis of the carbobenzoxy group (Z) and has been shown to be useful in the removal of this protective group from molecules such as small peptides and amino acids.[6] This catalyst can be easily regenerated for further use with no loss of catalytic activity. In this work, a continuous recycled loop system through a Pd−PEI catalytic column appears to improve dramatically the rate of hydrogenation with high yields of the desired soluble monoprotected poly(ethylene)glycol derivatives.

Experimental Section

Boc-PEG-Z and Boc-PEG-Boc (PEG's derivatives MW 1900) were prepared and characterized in our laboratory according to our own protocols.[1] Palladium−poly(ethylenimine) (Pd−PEI) beads (20−40 mesh) and palladium black were obtained from Aldrich. Chloroform, methyl alcohol, and formic acid, all reagent grade, were also obtained from Aldrich.

Catalytic Removal of the Benzyl Protective Group Z. Palladium−poly(ethylenimine) in methanol was poured into a 2 mL chromatography column. 2 g (~1 mmol) of the mixture, consisting of Boc-PEG-Boc and Boc-PEG-Z, was dissolved in a 4.4% formic acid−methanol solution at about 5 mg/mL. The solution was allowed to flow slowly through the column (2 mL/min) in a continuous recycled loop for a period of 4 h under a nitrogen atmosphere. The rate of catalyzed hydrogenolysis of the Boc-PEG-Z and Boc-PEG-Boc mixture was monitored by measuring the rate of deblocking of the amino group in the resulting monoprotected derivative Boc-PEG-NH_2 using the 2,4,6-trinitrobenzenesulfonic acid method (TNBS test).[7] An additional bed volume of formic acid−methanol was passed through the column to ensure complete removal of sample from the column. The eluent was evaporated under reduced pressure. To prevent breakdown of the Boc-PEG-NH_2 and Boc-PEG-Boc, the mixture once evaporated and crystallized, was diluted with water, partially evaporated at reduced pressure and then extracted into ethyl acetate.[5] After evaporation of the solvent a white solid material was obtained. A similar experiment was performed with the same mixture on palladium black as a catalyst, to compare the efficiency of the two systems.

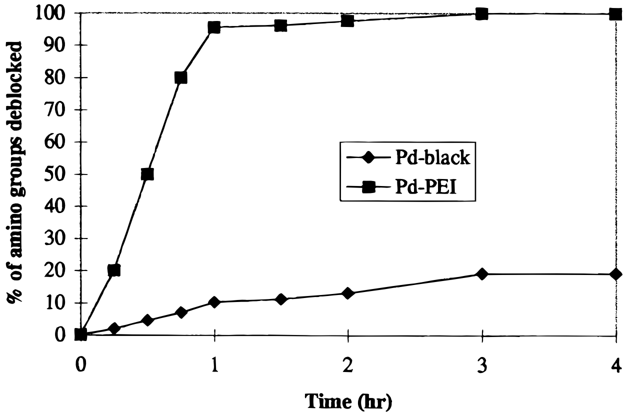

Figure 1. Rate of hydrogenation of the biprotected poly(ethylene)glycol derivative Boc-PEG-Z. The % of deblocked amino groups was measured during the experiment by taking samples of the solution from the continuous loop through the column at time intervals of 25 min.

Results and Discussions

The rate of catalytic cleavage of the carbobenzoxy group (Z) of the biprotected poly(ethylene)glycol derivative Boc-PEG-Z with Pd−PEI was more effective when compared with the rate observed with Pd-black. Figure 1 shows the results of both catalytic systems. The deblocking with Pd−PEI was almost complete (>95%) in 1 h, while Pd-black provided less than 50% deblocking. As evidenced by IR analysis, in all the experiments with Pd−PEI and Pd-black the second protective group (Boc) was not removed from the derivatives. The Boc group was removed selectively with TFA in subsequent bifunctional preparations. The utility and relevance of the Pd−PEI catalytic hydrogenation in this work is their effectiveness in removing protective groups when they are coupled to relatively large linear polymers (e.g., PEG's). These results compared favorably with literature reports where Pd−PEI has been used to remove the same type of protective group from small peptides and amino acids.[6] The great activity of Pd−PEI catalyst compared to Pd-black could be possibly due to the distribution of Pd on the large surface area available with PEI. The high rate has been also explained in terms of the possible attraction of the formic acid to the PEI matrix.[5]

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