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Study of the quantitative aminolysis reaction of poly(β-benzyl L-aspartate) (PBLA) as a platform polymer for functionality materials

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Dedicated to Professor Teiji Tsuruta on the occasion of his 88th birthday (Beiju).

Abstract

A facile and quantitative aminolysis of poly(β-benzyl L-aspartate) (PBLA) as well as the solution properties of the prepared cationic polyaspartamide were investigated in this study. The reaction was found to proceed in good yield without undesired side reactions via the formation of a succinimide intermediate in the polymer backbone, which was efficiently converted to polyaspartamide accompanying the α,β isomerization of the main chain. The polarity of solvents and the secondary structure of the polymer strand were closely related to each other in terms of reactivity and stereoselectivity. The aminolysis of PBLA treated with one equivalent amine against benzyl ester groups resulted in the complete conversion at 35 °C in random-coil solvents within 1 h. The racemization that accompanied this reaction was observed in random-coil solvents, but was efficiently suppressed in helicogenic solvents, with 95% of the optical purity maintained in CH_2Cl_2. In addition, the quantitative introduction of *N*,*N*-diisopropylethylenediamine (DIP) led to the formation of cationic polyaspartamide, poly[*N*-(*N*′,*N*′-diisopropylaminoethyl)aspartamide] (PAsp(DIP)), which showed pH and thermo-sensitivities in aqueous media. This systematic investigation of the aminolysis of PBLA with DIP demonstrates the feasibility of a PBLA-aminolysis system for designing functionalized polyaspartamides which can be useful as biomaterials.

Keywords: PBLA; Aminolysis; Quantitative side-chain reaction; Succinimide; Suppression of racemization; pH and thermo-sensitivities

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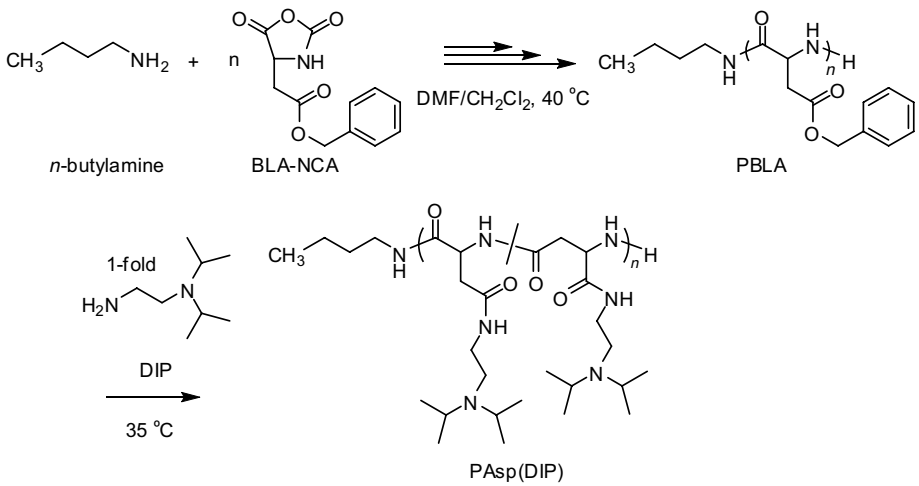

Scheme 1. Synthetic procedures of PBLA and PAsp(DIP) by the successive aminolysis reaction of PBLA.

1. Introduction

Chemical modification by the side-chain reaction of polymer is a convenient way to prepare a variety of functionalized derivatives from a single platform polymer [1–3]. For example, the precursor polymers bearing functional groups such as active ester [4–9], (meth)acryl chloride [10–12], and alkyne [13,14] are typical representatives with a potential for further functionalization or versatile modification according to particular applications. As a rule, the side-chain reaction was considered a facile synthetic route to obtaining polymer analogues with a constant degree of polymerization (DP) and molecular weight distribution (MWD) from a single platform polymer. Thus, the use of precursor polymer as a common intermediate allows for combinatorial strategies, feasible for evaluating and optimizing the correlation between the polymer structure and function.

There have also been many examples in bio-related fields where poly(amino acid)s with high biocompatibility and low toxicity [15–18] were chemically modified to increase their feasibility by binding hydrophobic drugs [19], a hydrophilic ethylene glycol segment [20] and pilot molecules [21] into the side chain. Although there have been several studies on side-chain modification using poly(lysine) or poly(glutamate/aspartate) as a platform polymer, the side-chain reaction of these poly(amino acid)s does not proceed quantitatively. The conversion of all the flanking moieties of the precursor polymers requires extreme conditions such as a high concentration of reactant, high temperature and long reaction time, leading to side reactions such as the decrease of molecular weight (MW) by the cleavage of the amide linkages in the main-chain, as in the case of the aminolysis of Poly(γ-benzyl L-glutamate) (PBLG) [22,23]. Alternatively, poly(succinimide) has been investigated as a more active precursor to preparing the isomeric library of polyaspartamide by the quantitative introduction of the functional groups [24–29]. However, the synthesis of this active precursor has some drawbacks, including a long time reaction, high reaction temperature, and coloring of the obtained product [30,31], limiting the resultant polymer under control. Namely, the polymers are still highly heterogeneous, not only in terms of DP and MWD but also in terms of optical purity and composition of the functional units in the side chain [32,33].

In this regard, we have recently established that the flanking benzyl ester groups of poly(β-benzyl L-aspartate) (PBLA) undergo a quantitative aminolysis reaction with various primary amine compounds, thus offering a variety of polyaspartamides useful for designing polymeric micelles and vesicles as a biomaterial application [34–39]. Although it has been suggested that the mechanism of this unique aminolysis reaction is involved with the succinimidyl ring formation, the details have not yet been clarified. Thus, it is critical to obtain insight into the reaction mechanism, particularly from the standpoint of kinetics, and to identify the detailed structure of polyaspartamide in order to assess its feasibility for use as biomaterials. To this aim, we investigated the mechanism and kinetics of the aminolysis reaction of PBLA, focusing on both the α to β transition