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## Cross-Linking of Poly( $\alpha$ -amino Acids)

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### ABSTRACT

Poly(L-leucine) and poly(L-phenylalanine) cross-link with either 2,4-toluene diisocyanate or 1,6-hexane diisocyanate but no such cross-linking resulted for poly( $\gamma$ -benzyl-L-glutamate). The latter polymer cross-links, however, upon transesterification with diols.

The polymerization of racemic leucine N-carboxyanhydride with primary amines as initiators [1] does not lead to random copolymers with L- and D-units but to polymers with long L- or D-sequences (if not to homopolymers) as indicated by the relative polymerization kinetics [1], enzymatic sequence analysis [2, 3], and IR spectra of the polymers as compared to authentic poly(L-leucines) and poly(D-alt-L-leucines) [4]. In principle, such polymers should be separable by affinity chromatography as shown by the successful separation of R- and S-polyolefins on optically active polyolefin matrices [5].

We therefore tried to prepare cross-linked stereoregular poly( $\alpha$ -amino acids) for the use in chromatographic columns. Diisocyanates were chosen as cross-linking agents because of their proven ability to attack amide bonds in polyamides [6] under subsequent formation of allophanate groups.

Poly(L-leucine) and poly(L-phenylalanine) cross-linked easily with either 2,4-toluene diisocyanate or even the less reactive 1,6-hexanediisocyanate (see below). The resulting cross-linked polymers

TABLE 1. Cross-Linking of Poly( $\gamma$ -benzyl-L-glutamates) of Various Number-Average Degrees of Polymerization,  $\bar{P}_n$ , in Benzene (B), Dioxane (D), or N,N-Dimethylformamide (DMF) Solutions at Reflux with 1,6-Hexane Diisocyanate (HDI) or 2,4-Toluene Diisocyanate (TDI) as Cross-Linkers

| No.    | Polymer $\bar{P}_n$ | Concentration (g/mL) | Solvent | Cross-linking Agent | Ratio NH/NCO (mol/mol) | Catalyst | Reflux time (h) | Insoluble polymer (wt%) |
|--------|---------------------|----------------------|---------|---------------------|------------------------|----------|-----------------|-------------------------|
| 92-29  | 187                 | 1                    | B       | HDI                 | 50                     | Pyr      | 48              | 0                       |
| 92-29  | 187                 | 1                    | B       | TDI                 | 50                     | Pyr      | 48              | 0                       |
| 101-41 | 86                  | 2                    | D       | TDI                 | 100                    | -        | 5               | 0                       |
| 101-41 | 86                  | 2                    | D       | TDI                 | 100                    | DMF      | 24              | 0                       |
| 92-16  | 100                 | 2                    | DMF     | TDI                 | 100                    | DMF      | 48              | 0                       |
| 92-16  | 100                 | 2                    | D       | TDI                 | 1                      | Pyr      | 72              | 0                       |
| 92-16  | 100                 | 2                    | D       | HDI                 | 1                      | Pyr      | 72              | 0                       |
| 92-29  | 187                 | 2                    | D       | HDI                 | 1                      | Pyr      | 72              | 0                       |
| 85-35  | 315                 | 2                    | D       | TDI                 | 1                      | TBTC     | 24              | 0                       |
| 92-16  | 100                 | 2                    | D       | TDI                 | 1                      | NaH      | 24              | 2.3                     |
| 92-29  | 187                 | 2                    | D       | TDI                 | 2                      | NaH      | 24              | 3.1                     |
| 92-29  | 187                 | 2                    | D       | TDI                 | 0.1                    | NaH      | 24              | 10.1                    |
| 92-29  | 187                 | 1                    | D       | TDI                 | 0.02                   | NaH      | 4               | 20.6                    |
| 92-29  | 187                 | 2                    | D       | HDI                 | 0.02                   | NaH      | 24              | 25.5                    |
| 92-29  | 187                 | 1                    | D       | TDI                 | 1                      | NaH      | 2               | 45.6                    |

swell to approximately two times their dry volumes in appropriate solvents, such as poly(L-leucine) in benzene or poly(L-phenylalanine) in trifluoroacetic acid. The swollen polymers showed practically no weight loss after washing and drying. Furthermore, the recovered solvents exhibited no trace of polymer after evaporation.

Similar reaction conditions did not lead to cross-linked poly( $\gamma$ -benzyl-L-glutamate), however, although the solvent and catalyst type were varied (Table 1). Tributyltin chloride, often employed for the catalysis of isocyanate reactions [7], also failed to yield cross-linked products. Sodium hydride catalyzed reactions resulted in cross-linked poly( $\gamma$ -benzyl-L-glutamates). These polymers were brown materials, indicating some degradation. Furthermore, they were heavily cross-linked, as one might suspect from the initial amide/isocyanate ratio, because they did not swell in common solvents for poly( $\gamma$ -benzyl-L-glutamates).

Poly( $\gamma$ -benzyl-L-glutamates) can, however, be cross-linked through their ester groups, e.g., with 1,4-dihydroxybutane as cross-linking agent and zinc acetate as the catalyst. Ethylene glycol was less satisfactory than 1,4-dihydroxybutane, although hazy gels resulted from the reaction of poly( $\gamma$ -benzyl-L-glutamates) with both diols. These gels could be swollen to 2-3 times their original volumes.

The reason for the unsuccessful attempts to cross-link poly( $\gamma$ -benzyl-L-glutamates) with diisocyanates without degrading side reactions remains unclear. Most likely is a steric effect because the  $\text{CH}_2\text{CH}_2\text{COOCH}_2\text{C}_6\text{H}_5$  side group of the poly( $\gamma$ -benzyl-L-glutamate) is more bulky than either the  $\text{CH}_2\text{CH}(\text{CH}_3)_2$  side group of poly(leucine) or the  $\text{CH}_2\text{C}_6\text{H}_5$  side group of poly(phenylalanine). The ester side group of poly( $\gamma$ -benzyl-L-glutamate) could effectively shield the main chain amide bonds from an attack by the diisocyanates and thus prevent cross-linking. The same ester groups are, of course, easily accessible to transesterification reactions.

## EXPERIMENTAL

All poly( $\alpha$ -amino acids) were prepared by polymerization of their respective N-carboxyanhydrides with hexylamine following standard procedures.

### Reaction of Poly(L-leucine) with 1,6-Hexanediisocyanate

A mixture of 3.5 g (0.031 mol amide bonds) poly(L-leucine) with a degree of polymerization of approximately 110, 150 mL benzene, and 10 drops m-cresol were stirred at room temperature for 2 d until the polymer was completely dissolved. Two drops each of 1,6-hexanediisocyanate and pyridine were added, the mixture stirred for two more

days, heated until boiling, and gently refluxed for 12 h. The clear, soft gel was washed first with *m*-cresol and finally with diethylether. Yield: 3.0 g (86%).

### Reaction of Poly(L-phenylalanine) with 2,4-Toluene Diisocyanate

be more accurate (2-3% error) than conventional methods (~5-10% error). The rate of HCl loss from  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{Cl}$  termini is first order in HCl with an  $\Delta E_a$  of 19.1 kcal/mol in the 170-200°C range. This relatively low activation energy is most likely due to internal strain in the  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{Cl}$  endgroup. These studies quantitatively substantiate earlier conclusions in regard to the mechanism of endgroup formation in  $\text{BCl}_3$  cointiated isobutylene polymerization.

## INTRODUCTION

By understanding the mechanism of initiation, termination, and chain transfer in carbocationic polymerization, macromolecules with well-defined head and endgroups have recently been synthesized [1-5]. Thus isobutylene polymerizations cointiated by  $\text{BCl}_3$  yielded polyisobutylenes (PIB) carrying one or two  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{Cl}$  termini [1-3, 5].

Tertiary chlorine containing structures are known to be heat sensitive even at relatively low temperatures and tend to eliminate HCl [6-10].

In the course of our continuing mechanism studies concerning the polymerization of isobutylene, we have prepared PIB's with one and two  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{Cl}$  endgroups and employed a sensitive thermal dehydrochlorination method to determine quantitatively the HCl arising from these endgroups. Subsequently we used this endgroup determination method to calculate number-average molecular weights,  $\bar{M}_n$ , and to obtain independent confirmation as to the number of functional groups,  $\bar{F}_n$ , in the polymer.

## EXPERIMENTAL

### Polyisobutylenes

PIB's containing one  $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{Cl}$  terminus, Samples 1 and 2