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Functionalization of Suluble Polymers

1. Replacement of the Hydroxyl Groups of Poly(oxyethylene) by Amino Groups

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Summary

In a first example of the functionalization of soluble polymers the conversion of the hydroxyl groups of poly(oxyethylene) into primary amino groups has been studied. Starting from poly(oxyethylene), the preparation of the diphthalimido derivative via the disodium salt is described. From this regiospecific functionalized polymer the di(aminoethyl) poly(oxyethylene), which exhibits excellent solubility properties, can be obtained by polymeranalogous hydrazinolysis.

Introduction

The application of insoluble polymer supports to peptide synthesis showed the possibility to simplify organic chemical synthesis using a polymeric matrix (MERRIFIELD 1963). To overcome the disadvantages of the insoluble matrix the application of soluble polymers to peptide synthesis has been proposed (BAYER and MUTTER 1972, BAYER and GECKELER 1974, GECKELER and BAYER 1974a, 1974b, MUTTER 1978). The use of soluble polymers for the fixation of biological active molecules (WYKES et al. 1971, MARSHALL and RABINOWITZ 1976, HOLZBACH and BAYER 1977, ABUCHOWSKI et al. 1977) and as solubilizing agents for drugs (HOLT and THADANI 1963, BARNES et al. 1975, BATZ 1977) has been the subject of many investigations. For the attachment of pharmacological active compounds to soluble macromolecules we needed polymers with different functional groups. To this end, it is advantageous to introduce or to convert functional groups in preformed polymers with good solubility properties. This communication deals with the conversion of the terminal hydroxyl groups of poly(oxyethylene) into primary amino groups by polymeranalogous reactions.

Experimental

Poly(oxyethylene) (1)(m.w. 6000) was purchased from

0170-0839/79/0001/0427/$01.00

Fluka Feinchemikalien GmbH, Neu-Ulm.

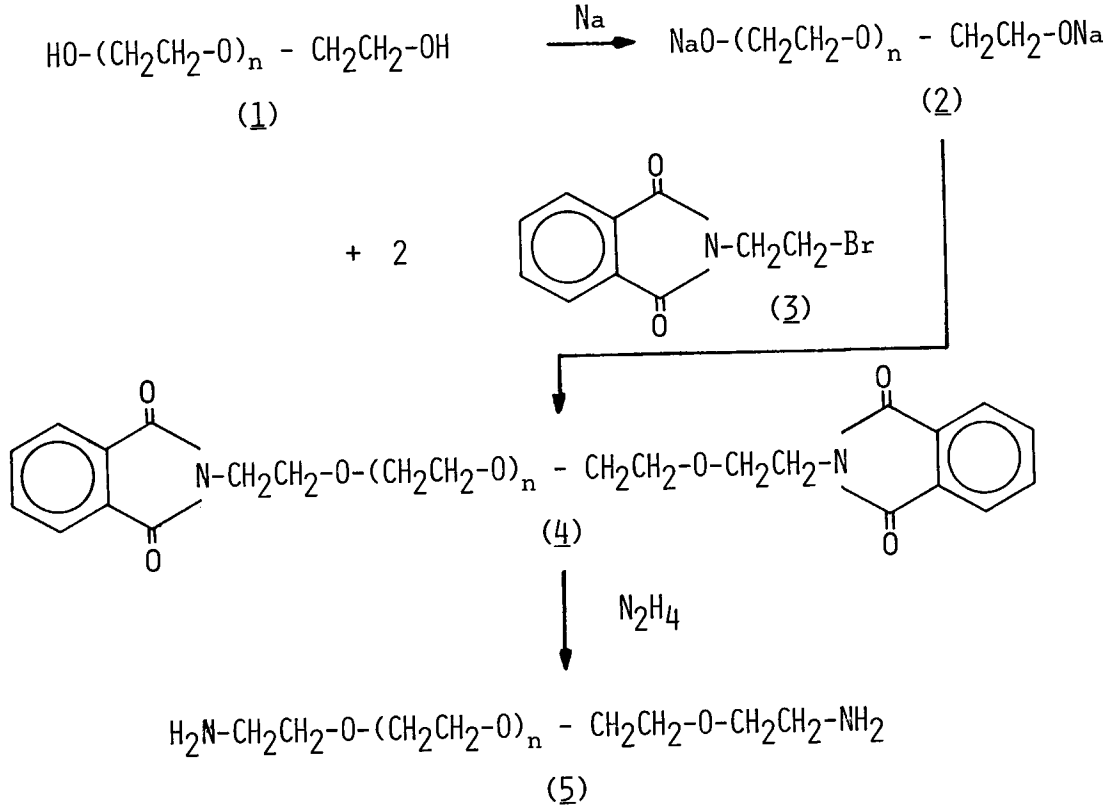
2-Bromoethyl phthalimide (3) was prepared by reaction of phthalimide with dibromoethane as reported elsewhere (SALZBERG 1932, DRAKE 1949). Yield: 77%, m.p. 82° C, R_F = 0.79 (benzene/ethanol, 1:1)

Di(phthalimidoethyl) poly(oxyethylene) (4). For purification poly(oxyethylene) (1) (technical grade) was dissolved in tetrahydrofuran, precipitated twice in diethylether (10fold excess) and thoroughly dried over phosphorus pentoxide at the oil pump. To a solution of (1) (12g) in 150 ml anhydrous tetrahydrofuran a suspension of sodium (550 mg, 50% in paraffin) in dry tetrahydrofuran (150 ml) was added under nitrogen and stirred for 2 h . The excess of sodium was filtered off, and a solution of 2-bromoethyl phthalimide (3) (10 g) in 100 ml dry tetrahydrofuran was added and stirred for one hour. After adding solid sodium iodide (0.2 g) and refluxing for 3 h, the mixture was cooled, filtered off and reduced to a volume of about 100 ml. (4) was precipitated by addition of ether (800 ml) under stirring. The mixture was cooled to 0° C, the polymer filtered off, and dried over phosphorus pentoxide. Yield: 10.1 g (80%),m.p. 57-58° C. IR (KBr): 2850 (ν C-H, ν C-N), 1650 (ν C=O), 1590 (ν C-Caromatic), 1470 (ν C-CH_2), 1100 (ν C-O-C) cm^{-1}.

Di(aminoethyl) poly(oxyethylene) (5). A solution of (4) (6.3 g) in a mixture of 50 ml hydrazine hydrate (100%) and 10 ml chloroform was kept for 4 days at 100° C. After evaporating the solvents in vacuo, the dry residue was dissolved in 50 ml benzene, filtered off, and precipitated from ether (600 ml). The obtained white powdery polymer was dried over phosphorus pentoxide in vacuo. Yield: 4.4 g (72%), m.p. 55-56° C. Complete separation from the excess reagents was controlled by thin layer chromatography (benzene/ether, 1:1), using ninhydrin as detecting reagent. The ^{1}H-NMR spectrum (in $CDCl_3$) showed the signal for the amino protons (δ = 1.59 ppm), whereas the hydroxyl protons of (1) (δ =2.08 ppm) have been disappeared. Both signals were recorded with a higher sensitivity. IR (KBr): 3500, 3400 (ν N-H), 2860 (ν C-H), 1580(ν N-H) 1460 (ν C-CH_2), 1100 (ν C-O-C) cm^{-1}.

Results and Discussion

Starting from poly(oxyethylene) (1), which is commercially available in a great variety of molecular weights (1500-20000) and exhibits good solubility in water as well as in numerous organic solvents, at


HO-(CH2CH2-O)n - CH2CH2-OH
(1)
Na
NaO-(CH2CH2-O)n - CH2CH2-ONa
(2)
+ 2
N-CH2CH2-Br
(3)
N-CH2CH2-O-(CH2CH2-O)n - CH2CH2-O-CH2CH2-N
(4)
N2H4
H2N-CH2CH2-O-(CH2CH2-O)n - CH2CH2-O-CH2CH2-NH2
(5)

first the disodium salt (2) was prepared. In order to introduce the nitrogen compound into the polymer chain, 2-bromophthalimide (3), which can be easily prepared from phthalimide and dibromoethane, was directly added to the solution of polymer (2) at room temperature. The resulting polymer derivative with two terminal phthalimidoethyl groups (4) represents "N-protected" di(aminoethyl) poly(oxyethylene) (5), which can be deblocked by polymeranalogous hydrazinolysis. In product (5) the aminoethyl group is fixed to the polymer backbone by a stable ether bond and continues therefore the constitutional repeating unit of the polymer chain. This hydrophilic polymer is soluble in many solvents, e.g. water, ethanol, pyridine, dioxane, benzene, dichloromethane, chloroform, and insoluble in diethylether and petroleum ether.

The structure of the polymers, depicted in the scheme of synthesis, was confirmed by spectroscopic data and chemical reactions. Titration as well as indirect determination of the amino groups by coupling an amino acid (t-butyloxycarbonyl alanine) with following cleavage and amino acid analysis (GECKELER and BAYER 1974a) showed an overall yield of 90% primary amino groups. The loading capacity of poly(oxyethylene) (0.1 - 1.3 mmole reagent per gramm polymer) depends primarily on the chain length of the polymer used (n= 35 - 500). On the other hand,it is possible to increase the loading capacity by attachment of multifunctional compounds.

This route for the preparation of soluble amino polymers represents two-step synthesis and can be applied on principle to all soluble macromolecules with hydroxyl groups. Depending on the structure of the modified polymer this procedure leads to two types of soluble polymeric products: (a) single-point or terminal binding, especially in the case of poly(oxyethylene), (b) multi-point binding of the low-molecular compounds on a macromolecule, in all cases of multifunctional polymers. Because of the regiospecific reactions polymeranalogous functionalization allows the preparation of polymers with well defined structure.

The flexibility of attaching and interconverting a wide variety of functional groups on a preformed soluble polymer is proposed to advantage for fixing many different types of compounds to the polymer.

Studies on the application of these functionalized soluble polymers will be reported in a separate paper.

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