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Soluble Polymers in Organic Synthesis
3. Polyethylene Glycol as Acid Labile Solubilizing Protecting Group+

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SUMMARY

The end function of polyethylene glycol was transferred to the tertiary alcohol for use as acid labile, solubilizing protecting group in peptide synthesis.

INTRODUCTION

Polyethylene glycols (PEG) are widely used for biomedical use as well as in organic synthesis due to their unique physical and chemical properties (Pillai and Mutter 1981). Specifically, when used as C-terminal protecting group in liquid-phase-peptide synthesis, PEG facilitates the reaction cycle in the step by step synthesis of peptides and exerts a solubilizing effect upon the peptide chain (Mutter and Bayer 1979). To make use of these advantages of PEG in organic synthesis, a wide range of easily splittable groups between PEG and substrate attached to its chain ends must be available (Pillai et al. 1980). As highly acid labile protecting group, we recently introduced the tert.-butylester analogue of triethylene glycol monomethylether (Anzinger et al. 1979). For practical reasons, the use of higher molecular weight PEG is indicated because of the high

+ For communication 2 in this series see: Mutter, M., Tetrahedron Letters, 2843 (1978)

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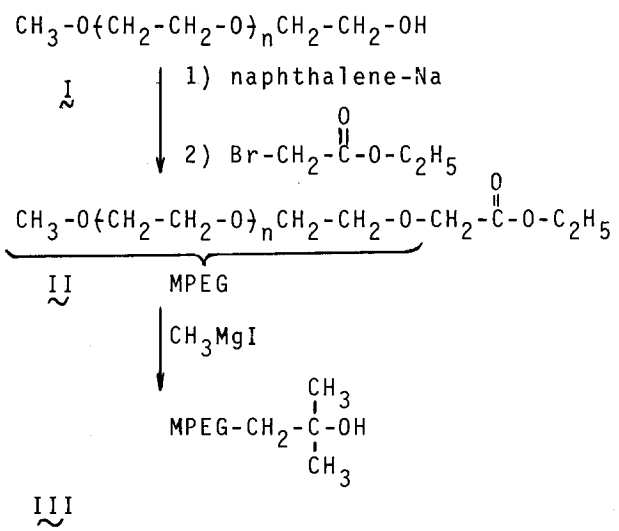
solubilizing effect and the tendency to crystallize from organic solvents.
Here we describe the modification of the chain ends of mono- or bifunctional PEG with $\bar{M}_n$ 2000 to the tertiary alcoholic group and its potential application as soluble carrier in organic synthesis as well as solubilizing protecting group in peptide synthesis.

RESULTS AND DISCUSSIONS

The procedure for transforming the primary OH of PEG to the tertiary OH group is outlined in Scheme 1.

Scheme 1:



I was titrated to the sodium alcoholate with naphthalene-sodium (Bückmann et al. 1980) and reacted with ethyl-bromoacetate to the PEG-ester II. By Grignard reaction II was converted to the tertiary alcohol III. Both reactions proceeded to quantitative yield, as proved by NMR, IR and t.l.c. As shown in Fig. 1, the ester triplet of II is replaced by a singlet (III) in the NMR spectra.

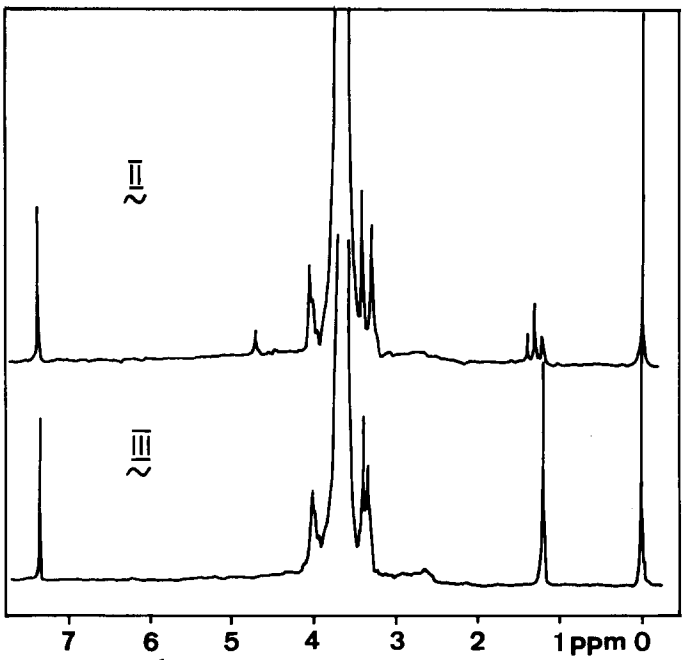


Fig.1. 90 MHz ^{1}H-NMR-spectra of II and III in $CDCl_3$

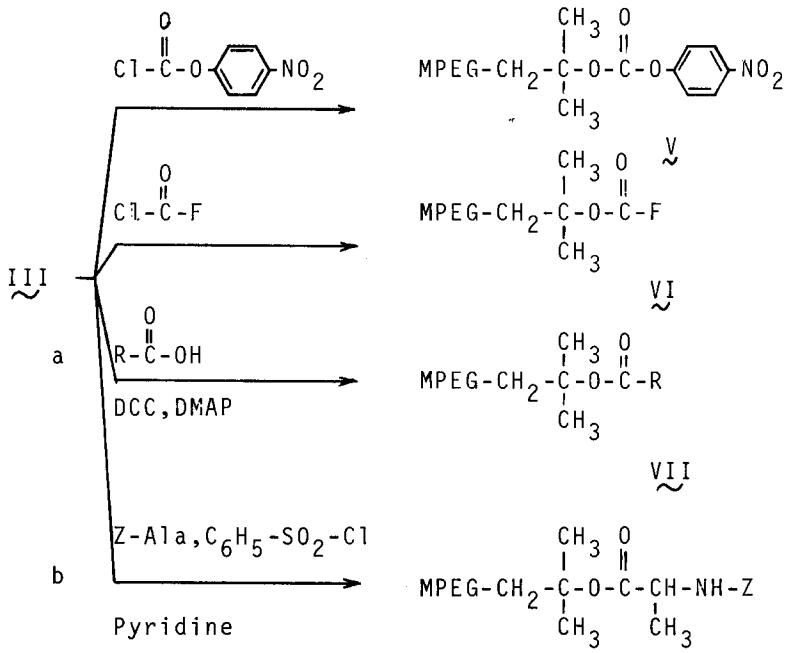
NH_2-protecting. The introduction of III into amines via urethanebonding results in an acid labile, temporary protecting group.This is readily achieved via the

(i) p-nitrophenylcarbonate
or (ii) fluoroformicester

as outlined in Scheme 2 .
The reaction with primary NH_2-groups proceeds generally under very mild conditions.
As a typical example, when VI was reacted with a 2-fold excess of the tripeptide-ester H-(L-Ala)$_3$-OMe the polymer peptide was obtained in practically quantitative yield. It proved to be readily soluble in organic solvents as well as in water.
Besides its use as solubilizing N-terminal (or side-chain) protecting group in peptide synthesis, this acid labile macromolecular protecting group may be

useful in the field of carrier supported pharmacological active compounds as well as in the modification of enzymes and proteins.

Scheme 2:



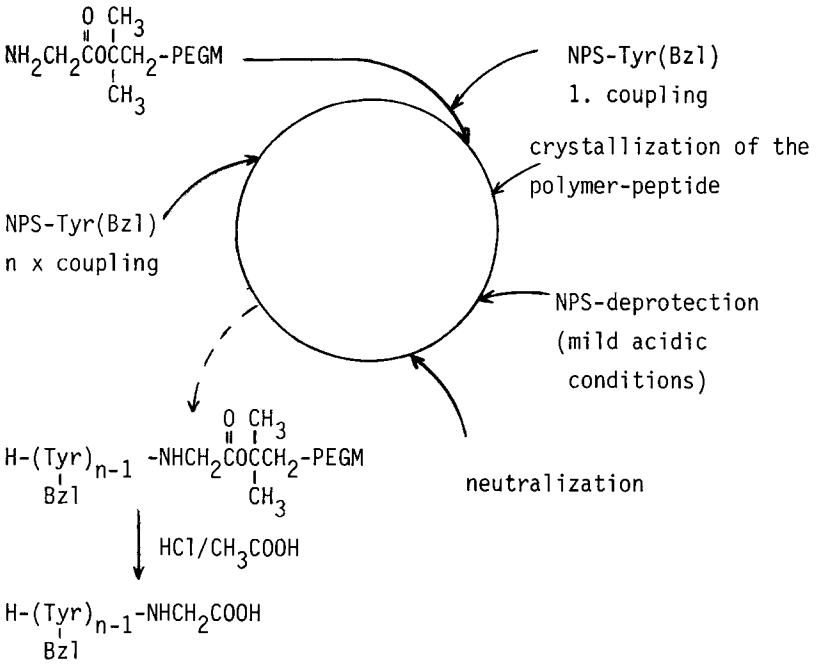
COOH-protection. When used as COOH-protecting group, III is esterified according to method a or b as outlined in Scheme 2. Method a is applicable for any COOH- containing compound, most notably for molecules with steric hindrance.

When used as a C-terminal protecting group in peptide synthesis, the danger of racemization during esterification in both methods might be a problem in some cases.

For example, oligo L-Tyr(Bzl) was synthesized stepwise for conformational investigations according to the liquid-phase-method (LPM) with C-terminal glycine (introduced by esterification of III with phthaloylglycine and subsequent phthaloyl deprotection by

hydrazinolysis) as an internal standard according to Scheme 3.

Scheme 3: Cycle of the stepwise oligo-L-Tyr(Bzl)-synthesis using a polymeric tert. butyl-ester as C-terminal protection.



Preliminary results show, that the acid stability of the bound substrates is significantly higher compared to low molecular tert. butyl groups due to the stabilizing inductive effect of a neighboring -O-CH_2-group. For obtaining acid labilities similar to low molecular weight tert.-butyl groups, the insertion of three CH_2-groups between ether oxygen and tertiary C-atom - i.e. of type -O-$(CH_2)_3$-$\overset{CH_3}{\underset{CH_3}{C}}$-OH via the acetoacetate method is under investigation.

EXPERIMENTAL

All solvents have been carefully dried. Reaction yields were tested by t.l.c. (silicagel plates, Woelm, F 254/366; solvent system CH_2Cl_2: CH_3OH = 7:1; Dragendorff-Bürger reagent).

α-Ethoxycarbonylmethyl-ω-methoxypoly(oxyethylene):
MPEG, $\bar{M}_n$ 1900 (30g=15.8 mmole) dried in vacuo over P_4O_{10}, was dissolved in 250 ml tetrahydrofuran at 60°. The polymer was reacted to the sodium alcoholate under dry nitrogen atmosphere by adding a sodium naphthalene solution prepared from naphthalene (20,2g=158 mmole) and sodium (3,63g=158 mmole) in tetrahydrofuran (50ml) under nitrogen at room temperature till the green color was stable for more than 5 minutes. Then 15,8g (95 mmole) ethyl-bromoacetate, dissolved in 10 ml tetrahydrofuran, were added dropwise.
After 2 hours stirring under dry nitrogen the reaction mixture was filtered over diatomaceous earth and concentrated in vacuo to a volume of ca. 100 ml. The polymer was precipitated under stirring by adding slowly 300 ml of dry ether, filtered and dried in vacuo over P_4O_{10}. 25g (80%) of α-Ethoxycarbonylmethyl-ω-methoxypoly(oxyethylene) were obtained.
NMR: triplet 1,18 ppm $-COO-CH_2-\underline{CH_3}$
IR: ν_{CO} 1752 cm^{-1}

α-Hydroxy-tert. butyl-ω-methoxypoly(oxyethylene):
II (24g=12 mmole) in 250 ml tetrahydrofuran was added dropwise to a freshly prepared solution of 120 mmole methylmagnesiumiodide in 150 ml of a 1:1 mixture of ether and tetrahydrofuran.
The mixture was refluxed for 2 hours and cooled to room temperature. The precipitated product was filtered, washed with ether and hydrolyzed in an iced NH_4Cl-solution. The aqueous phase was exhaustively extracted with dichloromethane, the collected organic

phases were washed with saturated NaCl solution and concentrated in vacuo to a volume of ca. 75 ml. The polymer was precipitated under stirring and ice-cooling by adding slowly 300 ml of ether, filtered and dried in vacuo over P_4O_{10}. 22g (92%) III were obtained.
NMR: singlet 1,08 ppm $-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-OH$

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