

## Synthesis of $\omega$ -mercapto-poly(alkylene oxide) by the Mitsunobu reaction

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**Summary** An efficient way to transform  $\omega$ -hydroxy-poly(alkylene oxide) in  $\omega$ -mercapto-poly(alkylene oxide) in two steps is described : the Mitsunobu reaction with thiolacetic acid followed by the reduction of the thiol ester. Yields are quantitative with water soluble polymers.

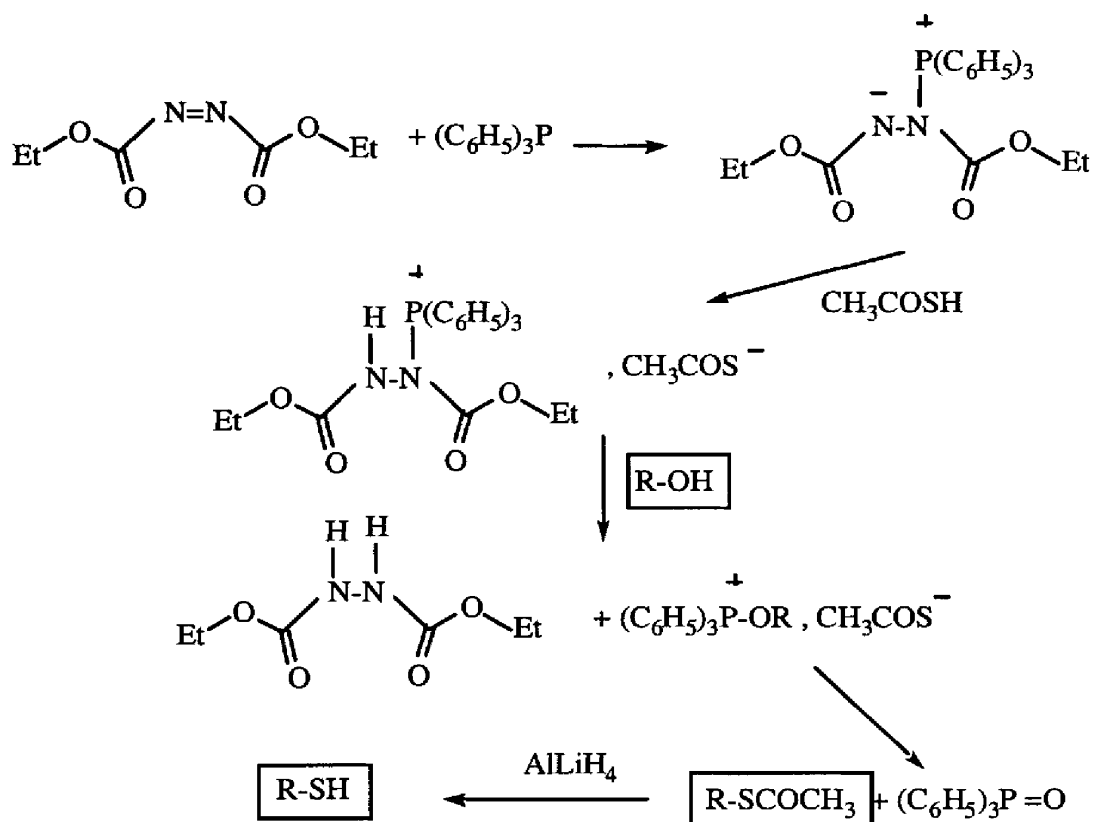
### Introduction

The dynamical properties of poly(propyleneoxide) PPO have been investigated in our laboratory by dielectric spectroscopy and dynamic mechanical measurements [1,2]. A comparative study between PPO and poly(propylenesulfide) PPS, has revealed the influence of hydrogen bonding on the dynamics, especially on the glass transition and the subglass relaxation[3]. In PPO, the substitution of the hydroxyl end groups by thiol end groups removes hydrogen bonding which modifies the dynamical behaviour of the polymer. The substitution allows the investigation of the influence of the hydrogen bonding, for the same chain backbone[4]. In order to realize this investigation, we needed to synthesise  $\alpha,\omega$ -dimercapto-poly(oxypropylene) : PPO-dithiol which was not described earlier in the literature. Tetra-thiol-functionalized poly(ethylene oxide) and poly(propylene oxide) were used in the synthesis of polymer networks[5], but neither the preparation nor the characterization of their structure have been published.

The interconversion of an hydroxyl into a thiol group is a well known problem in organic chemistry. Many reactions have been described[6,7,8] but some are not applicable for macromolecular chemistry. The modification of  $\alpha$ -hydroxy- $\omega$ -methoxypoly(oxyethylene) (POEME-2000) has been realized in different ways. These methods involve first the synthesis of POEME-Cl or POEME-OTs (TsO = tosylate) by substitution of the OH group. These compounds are then treated by the tetramethylammonium salt of a dithioacid[9] or different reactants such as : sodium hydrosulfide, thiourea, or trithiocarbonate[10] followed by thiol liberation. In all cases, disulfides, resulting from the oxidation of the thiolate by oxygen, are obtained with high yields : 90%[7] or 25 to 100%[5], and a reduction step is needed in order to give access to the thiols. The reduction conditions are not described in detail in these

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For our purpose, we considered in this paper another convenient method. The Mitsunobu reaction has a very broad range of applications in organic chemistry[11,12] and particularly thioesters can be obtained in one step from alcohols with high yields (Scheme 1). The reduction of thioesters with  $\text{AlLiH}_4$  gives thiols[13]. In addition, disulfides are also reduced in this second step. We describe in this paper some applications of the Mitsunobu reaction on PPO diol and triol and other commercially available hydroxy-telechelic polymers.



**Scheme 1** The Mitsunobu reaction and the reduction of thiol esters

## Experimental part

### Materials

Commercial polymers were used without further purification but dried in vacuum to remove water traces. The PPO-diol 425, PPO-triol 700, POE 2000 and Terathane® 2000 are purchased from Aldrich. The poly(ethylene glycol methyl ether) (POEME)350 and 750 are obtained from Acros. Triphenylphosphine and diethylazodicarboxylate (DEAD) were also commercial products. The Mitsunobu

reactions and the reductions were realized in anhydrous tetrahydrofuran (THF).

### *Reactions*

The Mitsunobu reactions were carried out according to the experimental considerations described in <sup>11</sup>. The DEAD-triphenylphosphine adduct is preformed in THF at  $-30^{\circ}\text{C}$  in an excess of 50% with regard to the alcohol functions. At this temperature, a pale yellow precipitate, corresponding to the DEAD-triphenylphosphine adduct, appears. A solution of polymer (1g) and thiolacetic acid (50 % excess) in THF is added dropwise. The precipitate disappears during this addition. The stirred mixture is allowed to warm to room temperature over four hours.. The reaction mixture is evaporated under vacuum in order to eliminate the solvent and the excess of thiolacetic acid. For water soluble polymers (POE 2000, MPEG 750) the mixture is dissolved in water and filtered off. The aqueous phase is washed with diethylether then evaporated and the residue is dried. For non water soluble polymers, at first, the reaction mixture is treated with a cyclohexane(75%)/ diethylether(25%) mixture to precipitate the diethyl hydrazinedicarboxylate. Then, after solvent evaporation, the product is treated with pentane (for soluble polymers) to precipitate the triphenylphosphine oxide. This process is repeated one or two times until the full elimination of the by-products. After evaporation of pentane, the raw  $\omega$ -acetylthiopolymers are reduced at room temperature by  $\text{AlLiH}_4$  (one mole of thiolacetate function for two moles of  $\text{AlLiH}_4$ ) in dried THF for one hour under a nitrogen flow. The reaction mixture is treated with a stoichiometric amount of 1N HCl, concentrated, and extracted with methylene chloride. The organic phase is dried, evaporated and the polymers are recovered.

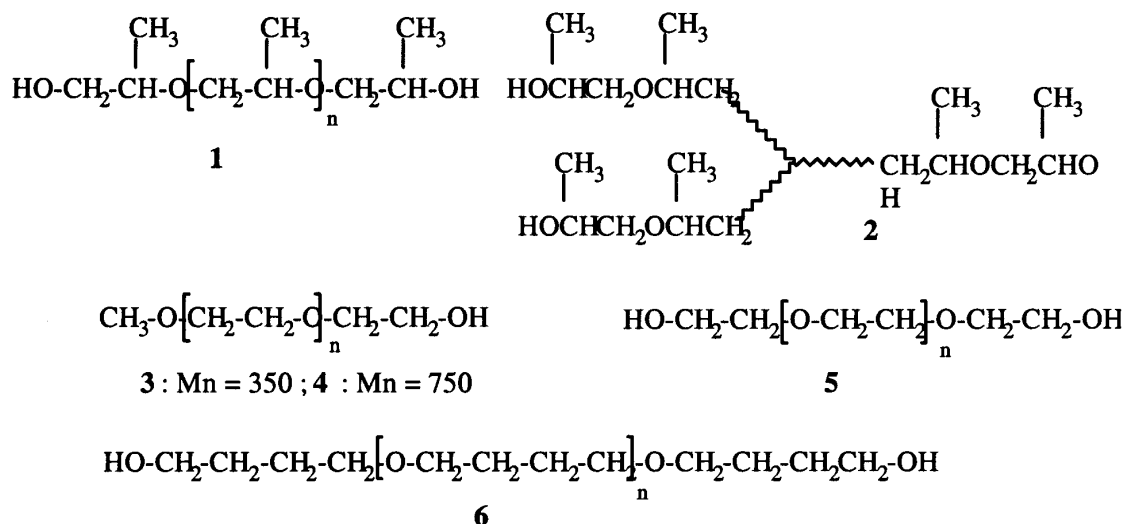
### *Instruments*

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC 400 spectrometer using TMS as the internal standard. Size exclusion chromatographies (SEC) were performed using a C5 Jordi gel column with refractive index detector.

### **Results**

In the Mitsunobu reaction described here, the poor hydroxy leaving group of an alcohol is transformed into a better oxyphosphonium leaving group through the redox reaction of triphenylphosphine/ diethyl azodicarboxylate. Subsequently, thiol esters are then obtained in an  $\text{SN}_2$  type displacement by nucleophilic thiol acetate. The four steps of the mechanism are reported in Scheme 1. Finally, the thiol esters are reduced by  $\text{AlLiH}_4$ .

The reaction was performed on six commercial hydroxylated polymers of four types : PPO diol-425 (1) and PPO triol-700 (2) , POEME-350 (3) and POEME-750 (4) ,  $\alpha$ -hydro- $\omega$ -hydroxypoly(oxyethylene) : POE 2000 (5) and poly(tetrahydrofuran) : Terathane® TE-2000 (6) (Scheme 2). Low molecular weight polymers were chosen in order to monitor and display the functional interconversion by  $^1\text{H}$  NMR spectroscopy.



### Scheme 2 Polymers used for the Mitsunobu reaction

In the experimental conditions described here, the conversions are nearly quantitative in both steps : the Mitsunobu reaction and the reduction. Triphenyl phosphine oxide and diethyl hydrazinedicarboxylate are by-products and the purification steps may lower the quantitative yield to 60-70% for non water-soluble polymers. For POEME 350 it was not possible to purify the polymer after reaction ; it is no more soluble in water and not soluble in pentane or cyclohexane. But for water soluble polymers, the yields after purification lie in the range : 90-95 %.

The interconversion of functional groups is observable on  $^1\text{H}$ NMR spectra. The hydroxyl group is at first transformed in a thiolacetoxo group and this group is further transformed in a thiol group. The modifications of the  $^1\text{H}$  NMR spectra corresponding to these transformations clearly appear in table 1. For all polymers, the hydroxy peak near 3 ppm, completely disappears and the singlet of the  $\text{CH}_3\text{COS}$  protons appears near 2.30 ppm. After the reduction, the SH peak is observed as a doublet near 1.85 ppm for PPO diol and triol and as a

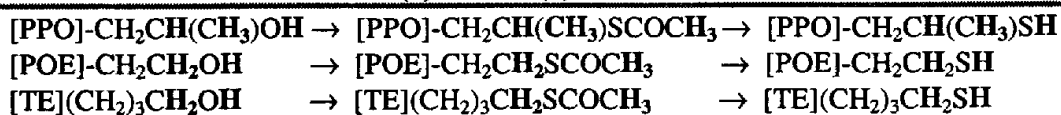
triplet near 1.6 ppm for POE and POEME ; the corresponding signal for TE is probably masked under the broad peak of the  $\text{CH}_2$ . A signal at 3.9 ppm characterizes the  $\text{CHOH}$  in PPO diol or triol ; it disappears in the acetylthio polymers probably in the broad signal of the  $\text{CH}_2\text{-CH}$  protons ; but the multicoupled signal of the  $\text{CH-SH}$  is visible at 3.09 ppm. The methyl group of PPO gives a narrow doublet at 1.05 or 1.10 ppm ; in the substituted PPO, a second doublet is present at low fields (1.25-1.30 ppm) corresponding to the methyl groups of the end-units. The hydroxymethyl hydrogens  $\text{OH-CH}_2$  in POE, in POEME and in TE are masked under the broad signal of the  $\text{CH}_2\text{O}$  ; in the acetylthiopolymers, the triplet characteristic of these protons shifts to higher fields and becomes observable at 2.85-3.15 ppm ; the substitution by the SH group induces for these protons another high field shift near 2.65-2.75 ppm and they appear in a six lines signal. The other parts of the spectra are not modified in these transformations. The complete disappearance of the OH groups and the occurrence of thiolacetoxo groups confirms the complete interconversion of alcohols in thiol esters and then in thiol end groups.

Modifications of the  $^{13}\text{C}$  NMR spectra confirm the functional interconversion. In PPO, the carbon signal of the  $\text{CH-OH}$  end group at 65.21 ppm in the diol and 66.8 ppm in

the triol is substituted by a new signal of the CH-SH at higher fields: 34.54 and 34.85 ppm respectively ; the carbon of the CH<sub>3</sub> end group is also sensitive to this modification : this signal 18.12 ppm in the diol and at 18.50 ppm in the triol shifts respectively at 20.46 and 20.72 ppm. In POEME and POE the carbon signals of the CH<sub>2</sub>OH end unit : 61.61 and 61.64 ppm respectively, are also substituted by other signals : 23.25 and 23.24 ppm.

**Table 1** Chemical shifts in ppm (TMS) and assignments of <sup>1</sup>H NMR spectra : (s) : singlet ; (d) : doublet ; (t) : triplet ; (m) : multiplet ; \* masked under other signals

Polymer		1	2	3	4	5	6
		PPOdiol	PPOtriol	POEME 350	POEME 750	POE	TE
	-OH	3.35	2.90	3.05	3.05	2.90	2.50 (ATFA)
ω-Hydroxy	-CH-OH						
	-CH <sub>2</sub> OH						
	CH <sub>3</sub> CH-O	3.97 (m)	3.90 (m)	*	*	*	*
		1.05 (d)	1.10 (d)				
ω-Acetylthio	CH <sub>3</sub> CO-S	2.30 (s)	2.35 (s)	2.32 (s)	2.37 (s)	2.35 (s)	2.30 (s)
	-CHS-CO-						
	-CH <sub>2</sub> SCO-						
	CH <sub>3</sub> -CHS	*	*	3.15 (t)	3.15 (t)	3.10 (t)	2.85 (t)
		1.25 (d)	1.30 (d)				
ω-Mercapto	-SH	1.87 (d)	1.85 (d)	-	1.60 (t)	1.65 (t)	*
	-CH-SH						
	-CH <sub>2</sub> -SH						
	CH <sub>3</sub> -CH-S	3.09 (m)	3.08 (m)	-	2.72 (m)	2.75 (m)	2.65 (m)
		1.27 (d)	1.28 (d)				



Analysis by size exclusion chromatography (SEC) (Table 2) indicate that no degradation occurs during the chemical modification. The chromatograms also exhibit the presence of other macromolecules in small amounts (5-10%) with a molar mass of exactly twice the starting one. These macromolecules are likely the corresponding disulfides, formed through thiol oxidation by oxygen traces in spite of a nitrogen flow during the reduction step. The polydispersity indices are slightly higher after modification on account of the presence of disulfides. However, the amount of disulfides does not increase with storage in the dark. An increase of the amount of  $\text{AlLiH}_4$  in the reduction does not modify the proportion of disulfides. For our purpose[4], the mixture thiol/ disulfide could be used without any drawback. In order to fully avoid the presence of disulfides, the air has to be fully excluded from the apparatus by evacuation in the reduction step.

**Table 2** Molar masses by SEC ( in polystyrene equivalent)

Polymer	$M_n$ (g.mol <sup>-1</sup> ) before reaction	$M_w/M_n$ before reaction	$M_n$ (g.mol <sup>-1</sup> ) after reaction	$M_w/M_n$ after reaction
PPO diol	647	1.02	658	1.06
PPO triol	880	1.02	942	1.07
MPEG 750	831	1.05	862	1.07
PEO 2000	2 152	1.03	2 131	1.04

We developed a new synthetic method to prepare conveniently  $\omega$ -mercapto-poly(alkylene oxide) in order to study the effect of H bonding on glass and sub-glass dynamics of PPO. There are potentially many applications of these  $\omega$ -mercapto polymers in organic synthesis (e.g. in liquid-phase synthesis[14]) as well as in macromolecular synthesis (e.g. block copolymers by chain transfer in free radical polymerizations).

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