

On the Possibility of Chemical Modification of Polyethylene Glycol in Melt

O.E. Philippova, I.N. Topchieva, and S.I. Kuchanov*

Department of Chemistry, Lomonosov Moscow State University, SU-119899 Moscow, USSR

Summary

The reactions between polyethylene glycol of molecular weights 1000-15000 and benzoyl bromide, acetic anhydride and dinitrofluorobenzene in melt have been studied. The advantage of chemical modification in melt, in comparison with that in solution, has been shown.

Introduction

The polyethylene glycol (PEG) derivatives synthesized by chemical modification of terminal hydroxyl groups have wide applications in biochemistry (as artificial antigens (1), soluble matrices in liquid phase synthesis of peptides (2,3), for separation of protein mixtures, viruses and some other biological objects (4,5), for the synthesis of drugs with prolonged action (6,7), etc.). Rather often, however, at the modification of PEG terminal groups, the functionality of synthesized compounds is appreciably lower than its theoretical value (8-10). This is, probably, explained by two main factors: a chemical factor and a physical one. The chemical factor involves the formation of hydrogen bonds between the chain hydroxyls and ether groups, affecting the PEG reactivity. The physical factor involves the polymer ability to crystallize from dilute solutions in organic solvents.

The detailed studies of PEG hydroxyl groups activity for the example of the model reaction of benzylation have shown (11) that the association of terminal OH-groups with oxygen atoms of the main chain weakly affects the PEG reactivity. This permits to claim that the chemical factor is not the main reason aggravating the polymer modification. Evidently the physical factors are crucial. The present paper gives the results of the studies how the physical factors affect the PEG reactivity and describes the synthesis optimum conditions for a number of this polymer derivatives, which are important for practical purposes.

Experimental

PEG of molecular weights (MW) 1000, 2000, 6000 and 15000 were used without preliminary purification. Pyridine was dried over KOH for five days and distilled over barium oxide at 388 K (12). Tributylamine was distilled over sodium at 489 K (12), benzoyl bromide was synthesized from benzoic acid

* To whom offprint requests should be sent

and phosphorus tribromide as in ref. (13). Acetic anhydride was distilled at 413 K (12). Dinitrofluorobenzene was vacuum dried over P_2O_5 at 330 K for 6 hours.

PEG dibenzoate of MW₃ 1000 in a melt was produced as follows. 0.9 ml (3.8×10^{-3} mole) of tributylamine and 0.24 ml (2×10^{-3} mole) of benzoyl bromide were added to 0.5 g of a melt PEG 1000 (10^{-3} mole of OH-groups) in a reaction vessel with a ground stopper. The reaction vessel was filled with nitrogen and put into a thermostat with temperature of 358 K for 10 minutes. When the reaction ended the polymer was purified from an excess of reagents by precipitation in diethyl ether. The purity of the synthesized PEG derivatives was controlled by thin layer chromatography on "silufol" plates in ethanol. The degree of conversion was determined by IR-spectroscopy by the intensity of the band of carbonyl₁ stretching vibrations in the reaction product at 1730 cm^{-1} , using the absorbance coefficient of the model compound, viz. ethylbenzoate. To estimate the width of the molecular-weight distribution (MWD) the polymer was analyzed using gel-permeation chromatography₂ (GPC) with Waters G-200, columns of styrogel (10^2 , 5×10^2 , 10^3 and 10^4 Å) tetrahydrofuran was used as an eluent.

The other PEG derivatives in melt were obtained by a similar technique. The table lists the conditions of the synthesis and molecular weight characteristics of reaction products.

Results and Discussion

PEG of molecular weight above 3000, similarly to other polymers of regular structure, i.e. polyethylene (14), polypropylene (15), can crystallize from dilute solutions in organic solvents. Studies of solutions of these polymers show (14-16) that the formation of regular elements of a solid starts already in solution and manifests itself by the appearance of aggregates of macromolecules of different morphology depending on the solvent quality, on MW and temperature of crystallization. Evidently, the reactivity of macromolecules in the supermolecular structures must considerably differ from that in homogeneous solutions. Actually, it is shown (17) by the example of polyethylene chlorination in CCl_4 , that the degradation of the polymer solubility results in a drastic retardation of the reaction not permitting to carry out chlorination to high degree of conversion.

The analysis of the literature shows that at the choice of PEG concentrations for its chemical modifications authors have not taken account of the possibility of polymer crystallization. Diminished functionalities of PEG derivatives, probably are the result of processes of microstructuring of the polymer in organic solvents.

Therefore, for obtaining high degrees of conversion homogeneous solutions must be used for PEG chemical modifications. The range of PEG concentrations corresponding to homogeneous conditions must be determined accurately on the basis of phase diagrams of the polymer state in the solvent used. However, for the system PEG-organic solvent such data are not available. Our preliminary estimates of PEG solubili-

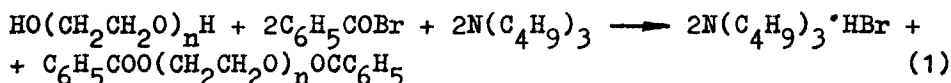
Table

The conditions of the reaction of PEG acylation in melt at 358 K and the characteristics of the reaction products

MW of PEG	Reaction	Ratio of reagents OH-groups: acylating agent: amine	Reaction time, min	Yield, %	Functionality	M_n	M_w	M_w/M_n	$(M_w/M_n)_{orig}$
1000	(1)	1:2:4	10	96	2.0	960	980	1.02	1.01
1000	(2)	1:2:4	5	97	2.0	960	980	1.02	1.01
3000	(1)	1:6:20	40	98	1.9	2550	2750	1.08	1.08
3000	(2)	1:6:20	15	98	2.0	2450	2600	1.06	1.08
6000	(1)	1:6:20	50	99	-	5230	6540	1.25	1.08
6000	(2)	1:6:20	40	99	1.9	6000	6400	1.06	1.08
6000	(3)	1:3:50	30	99	1.75	6030	6500	1.08	1.08
15000	(1)	1:6:20	90	99	-	9840	15800	1.61	1.20
15000	(2)	1:6:20	60	99	1.9	13300	15600	1.17	1.20

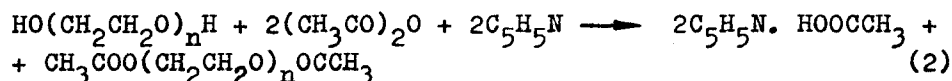
ty in CCl_4 and dioxane have shown that homogeneous conditions can be created only for sufficiently dilute solutions (to 10^{-2} mole/l), but their use for polymer chemical modification is inconvenient for preparative treatment.

Undesirable effect of physical factors may be excluded if the reaction is carried out in the absence of solvent, viz. in a melt. The low melting point of PEG (equal 329-330 K (18)) is favourable for such a reaction. The only example we know of the reaction of PEG terminal hydroxyl groups in melt is three dimensional polycondensation with diisocyanate when triisocyanate is used as a cross-linking agent (19). It should be noted that in PEG melt most OH-groups participate in the formation of hydrogen bonds with ether oxygen atoms of the main chain (20). However, the literature (20) does not give any information on types of H-complexes in melt and on their quantitative ratio. Nevertheless, it can be concluded, that hydrogen bonds are retained in melt. The main effect of melt is the creation of high concentration of reagents allowing to increase considerably the reaction rate and thus to decrease the reaction time. For example, reaching 90% conversion when PEG dibenzoate of MW is produced in CCl_4 by reaction (1), takes about 60 hours, while the similar process in melt takes 5 minutes (see the table).



Let us consider in more detail the specific features of the reaction occurring in melt. First of all PEG interaction with benzoylbromide in the presence of tributylamine has been studied (1). It is shown that for polymers of MW 1000, 3000 reaction proceeds in 10-40 minutes, the derivatives produced are characterized by functionality close to the theoretical one and by narrow MWD (table). Simultaneously when PEG dibenzoates of large MW (6000, 15000) are synthesized an appreciable destruction of the polymer is observed. To elucidate the reasons of this phenomenon, model experiments on studies of molecular weight characteristics of PEG of MW 15000 with and without tributylamine have been carried out. It is shown that in both cases melting does not result in polymer destruction. But, it is known that hydrogen bromide released in the reaction can destroy the PEG polymer chain (21). Evidently, destruction is related to the absence of complete compatibility of reagents, the compatibility degrading with increasing PEG MW. As a result PEG and tributylamine are in different phases, therefore amine cannot fulfill the function of hydrogen halide acceptor with sufficient efficiency.

Since compatibility of reacting substances considerably affects the reaction course, later we used modifying agents providing complete mutual solubility of the melt components. That was the PEG - acetic anhydride - pyridine system (2)

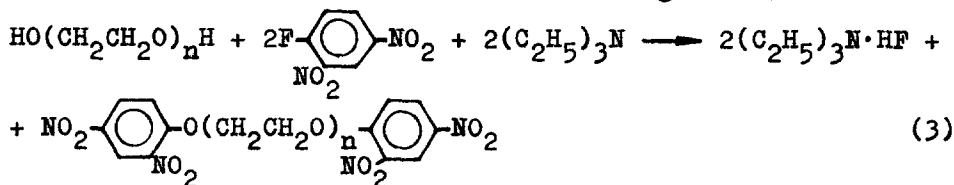


The reaction (2) conditions and molecular-weight characte-

ristics of PEG derivatives produced are listed in the table. As it is seen in a homogeneous medium polymer destruction does not occur until MW 15000.

Thus, the suggested method of PEG chemical modification in melt decreases the reaction time and provides high degree of conversion, while retaining constant polymer molecular-weight characteristics. The method is developed for the acylation reaction which is widely used (22) for the determination of PEG MW by the concentration of terminal functional groups. In addition, PEG acylation products have found application in biochemistry as soluble matrices in liquid phase synthesis of peptides (3).

The method of PEG terminal functional group modification in melt can be extended for synthesis of other PEG derivatives with valuable properties. Using this method we have synthesized (reaction 3) 2,4-dinitrophenyl derivatives of PEG which are known as artificial antigens (1).



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