THE REACTION OF POLYMERS OF 2,3-EPOXYPROPYL METHACRYLATE WITH N-(BENZYLOXYCARBONYL) GLYCINE AND GLYCINE TERT-BUTYL ESTER

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The reaction of the epoxy groups of polymers of 2,3-epoxypropyl methacrylate with N-(benzyloxycarbonyl) glycine in N,N-dimethylformamide and the reaction with glycine tert-butyl ester in benzene in the presence of 4-nitrophenol at 80°C were investigated. The rate constants were calculated for the reaction with N-(benzyloxycarbonyl) glycine. The reaction of macroporous gels of 2,3-epoxypropyl methacrylate–ethylene dimethacrylate with N-(benzyloxycarbonyl) glycine was studied.

Polymers most frequently used in the investigation of reactions of oxirane groups on polymers are polymers of 2,3-epoxypropyl esters of unsaturated acids[1-3], mainly 2,3-epoxypropyl methacrylate, acrylate, crotonate or epoxidized polybutadienes[4,5]. Iwakura and coworkers investigated reactions of copolymers of 2,3-epoxypropyl acrylate with various amines[6-8]. Kakurai and coworkers investigated the effect of various comonomers in copolymers of 2,3-epoxypropyl methacrylate on the reaction rate with amines[9]. Also reactions of the oxirane group with carboxyl were studied on 2,3-epoxypropyl methacrylate polymers[10-12].

Polymers and copolymers of 2,3-epoxypropyl methacrylate may also be employed in the binding of biologically active compounds[13-15]. Reactions of the epoxy groups of the polymer with the amino group, carboxyl, hydroxyl or the mercapto group of biologically active compounds may be considered for this purpose. Reactions between the epoxy groups and the amino and carboxyl group were studied using a model reaction: 2,3-epoxypropyl pivalate[16] was chosen as the model for polymers of 2,3-epoxypropyl methacrylate, and the kinetics of reactions with N-(benzyloxycarbonyl) glycine and glycine tert-butyl ester were measured[16]. After that we passed to the high-molecular weight system.

This paper is dealing with reactions of the oxirane groups of polymers of 2,3-epoxypropyl methacrylate and N-(benzyloxycarbonyl) glycine in N,N-dimethylformamide and with the reaction with glycine tert-butyl ester in benzene in the presence of 4-nitrophenol. The reaction between macroporous gels of 2,3-epoxypropyl methacrylate–ethylene dimethacrylate and N-(benzyloxycarbonyl) glycine was also investigated.

TABLE I

Composition of the Mixture for Solution Copolymerizations of 2,3-Epoxypropyl Methacrylate (monomer) in Benzene (60°C) Initiated with 2,2'-Azobis(isobutyronitrile) and Characteristics of the Products

Copolymer (polymer)	Composition of the mixture, mass %				Reaction time, h	Composition of the copolymer mol.%		$M_n \cdot 10^{-4}$	$M_w \cdot 10^{-4}$
	monomer	comonomer	initiator	solvent		monomeric unit	comonomeric unit		
				Comonomer: styrene					
I	7·64	22·31	0·23	69·82	7	28·7	71·3	2·75	6·7
II	14·27	15·68	0·15	69·90	5	46·5	53·5	4·18	9·3
III	20·08	9·86	0·20	69·86	3·5	53·9	46·1	4·50	9·6
				Comonomer: methyl methacrylate					
IV	11·33	18·59	0·22	69·86	1·75	33·5	66·5	9·65	29·4
V	18·82	12·19	0·21	68·78	1·50	55·1	44·9	14·00	20·8
VI	24·26	5·69	0·19	69·87	1·25	73·4	26·6	15·30	23·2
				Comonomer: —					
VII	34·13	—	0·47	65·40[a]	1[b]	100·0	—	11·40	29·0

[a] 1,4 — Dioxane, [b] 70°C.

EXPERIMENTAL

Compounds

2,3-Epoxypropyl methacrylate was prepared by a modified procedure[2] from potassium methacrylate (1 mol) and 1-chloro-2,3-epoxypropane (9 mol) in the presence of tetramethylammonium chloride (6 mmol) and 4-(1,1,3,3-tetramethylbutyl) pyrocatechol (9 mmol). The raw monomer was rectified in nitrogen on a column 1/2 m long packed with Heli-Pak. Yield 85% theor.; b.p. 36°C/27 Pa, n_D^{20} 1·4510 (ref.[17] b.p. 62°C/0·4 kPa; n_D^{20} 1·4501). Purity according to GLC: 98·6%. Content of epoxy groups[16]: 99·5%.

The preparation of N-(benzyloxycarbonyl) glycine and glycine tert-butyl ester has been described in ref.[16].

Styrene (Kaučuk, Kralupy) was purified by employing a standard procedure[18]. It was rectified before use in nitrogen on a column 1/2 m long packed with Heli-Pak. The fraction having b.p. 45·7°C/2·7 kPa was used; n_D^{25} 1·5440 (ref.[19] n_D^{25} 1·5439). Purity according to GLC: 99·8% Methyl methacrylate (Synthesia, Pardubice) was purified by employing the same procedure as that used for styrene. The fraction used had b.p. 46·5°C/13·9 kPa; n_D^{20} 1·4138 (ref.[20] n_D^{20} 1·4142). Purity according to GLC: 99·7%. Ethylene dimethacrylate (Dental, Prague) was purified by a modified procedure[21]. The ester was diluted by the same amount of hexane, shaken several times with a 10% solution of sodium hydroxide and washed with a 5% solution of sodium chloride to neutral reaction. After the extract had been dried with anhydrous magnesium sulphate, hexane was evaporated on a rotational vacuum evaporator. The residue was stabilized with a mixture of Cu(I) chloride and 4-(1,1,3,3-tetramethylbutyl)pyrocatechol and rectified in nitrogen on a Vigreux column, 1/2 m long, b.p. 78°/93 Pa.

The other chemicals and solvents used were reagent grade or were purified or dried by employing standard procedures. The dried solvents were stored over activated molecular sieves in an inert atmosphere.

Polymerization and Characterization of Polymers

A solution of monomeric mixture (30% by mass) was prepared, and 2,2'-azobis(isobutyronitrile) (0·5 mol.% per total amount of monomers) was added to it; the composition of mixtures is given in Table I. The polymerizations were carried out at 60 ± 0·1°C in evacuated ampoules (*c.* 10^{-3} Pa) roughly to a 15% conversion. The polymer was precipitated with stirring into a thirtyfold volume of methanol, separated and dried to constant weight at room temperature and *c.* 15 Pa. The polymers were reprecipitated. Their composition was determined by the argentometric titration of epoxy groups[16]. The number average molecular mass M_n was measured with an automatic membrane osmometer Knauer (FRG); the mass average molecular mass M_w was determined by light scattering from a photogoniodiffusometer Sofica (Fica, France).

Kinetic Measurements

The reactions of polymers with glycine derivatives were carried out in DMF at 80 ± 0·1°C by employing a procedure described in ref.[16]. The reaction course was investigated by the method of gel permeation chromatography using the concentration loss of glycine derivatives.

Gel Preparation

The gels were prepared by a modified procedure[22]. The composition of the copolymerization mixture is given in Table II. The suspension copolymerization proceeded 2 h at 60°C, and another 10 h at 70°C. After completion of the reaction, the mixture was stirred (4 rps) until fully cooled. The soluble components were removed by washing with water, methanol and benzene. The gel was dried at room temperature and *c.* 70 Pa. Dry gels were resifted on stainless sieves, and the fraction with the diameter 0·200—0·315 mm was used in the reaction with N-(benzyloxycarbonyl) glycine. The specific surface of gels was determined by the BET method on a Quantasorb apparatus (Quantachrome, USA).

RESULTS AND DISCUSSION

The composition of copolymers of 2,3-epoxypropyl methacrylate with styrene (*I*–*III*) and methyl methacrylate (*IV*–*VI*) and the M_n and M_w values (including those of poly(2,3-epoxypropyl methacrylate)) are given in Table I. For the reaction of epoxy groups of these polymers with N-(benzyloxycarbonyl) glycine in DMF at 80°C it may be assumed that similarly to the model reaction[16] of 2,3-epoxypropyl pivalate with N-(benzyloxycarbonyl) glycine only one reaction product is formed. The results of measurements of the reaction courses were evaluated using the least squares method from the integral form of the second-order kinetic equation. In the case of copolymers *I*–*III* the dependences $(a - b)^{-1} \ln [b(a - x)/a(b - x)]$ or $x/a(a - x)$ on time were linear roughly to a 25% conversion of epoxy groups; for copolymers *IV*–*VI* and polymer *VII* the linearity was observed to an approx. 60% conversion. Two reactions seem to proceed simultaneously, namely, a normal bimolecular reaction and a reaction catalyzed by the hydroxy group arising in the reaction.

Each epoxy group present, if not sterically protected, may undergo the bimolecular reaction. On the other, hand of course, only some groups may undergo the reaction facilitated by the presence of the hydroxy group. Iwakura and coworkers[6] believe that only hydroxy groups on the same chain as the reacting epoxy group, which moreover must not be too far, can participate in the autocatalytic effect. It must be

TABLE II

Specific Surface of Gels of 2,3-Epoxypropyl Methacrylate–Ethylene Dimethacrylate

Initial copolymerization mixtures: 40 g monomer, 40 g comonomer, 600 g water, 0·8 g 2,2′-azobis(isobutyronitrile), 6 g poly(vinylpyrrolidone), chosen quantities of cyclohexanol and 1-dodecanol. [M] denotes the participation of monoester units in the gel.

Gel	Cyclohexanol g	1-Dodecanol g	[M] mol.%	Spec. surface $m^2 g^{-1}$
1	100	—	46·5	79·7
2	90	10	46·9	95·3
3	70	30	43·5	53·3

admitted, however, that also epoxy groups from another chain may get into close vicinity of the hydroxyl, thus taking part in the autocatalytic reaction. All the reactions proceeded to an approx. 90% conversion of epoxy groups; this means that 10% of all the epoxy groups present were sterically inaccessible to the agent. If the rate of the uncatalyzed reaction of 2,3-epoxypropyl pivalate with N-(benzyloxycarbonyl) glycine ($4 \cdot 96 \, . \, 10^{-4}$ l mol^{-1} min^{-1}) is compared with those of the reactions on polymers (Table III), one can see that former are higher than those of the model reaction.

TABLE III

Rate Constants of the Reaction of 2,3-Epoxypropyl Methacrylate Polymers with N-(Benzyloxycarbonyl) Glycine at 80°C in DMF

Copolymer (polymer)	Initial concentration of components, mol l^{-1}		$k \, . \, 10^4$ l mol^{-1} min^{-1}
	derivative of glycine	epoxy groups	
I	0·3088	0·2803	6·24 ± 0·35
II	0·2789	0·2564	9·63 ± 0·29
III	0·3243	0·2818	8·91 ± 0·17
VI	0·2794	0·2767	41·4 ± 2·1
V	0·2771	0·2771	40·56 ± 0·69
VI	0·2775	0·2772	33·2 ± 2·8
VII	0·2789	0·2792	32·6 ± 2·5

TABLE IV

Composition of Initial Mixtures and Conversion of the Epoxy Groups of Gels (Table II) in the Reaction with N-(Benzyloxycarbonyl) Glycine (80°C, DMF)

Gel No	Weighed amount, g		Conversion of epoxy groups, %		
	gel	amine[a]	24 h	48 h	72 h
1	0·1992	0·0109	5·1	16·9	28·8
2	0·2002	0·0116	9·5	22·6	37·2
3	0·2007	0·0105	2·9	11·9	24·4

[a] Values recalculated from the known weighed amount 0·0880M of the stock solution.

In the reaction of the epoxy groups of polymers with glycine tert-butyl ester in the presence of 4-nitrophenol as catalyst, the second hydrogen atom of the amino group also reacted immediately at 80°C in benzene, unlike the model reaction[16] between 2,3-epoxypropyl pivalate with glycine tert-butyl ester. The samples became more viscous and turned into gels after three hours of the reaction.

It was moreover observed qualitatively that glycine tert-butyl ester was sorbed on the polymer, both in the presence and in the absence of 4-nitrophenol[23]. These facts prevented us from a quantitative evaluation of the reaction. Obviously due to sorption, the concentration of glycine ester considerably increases in the neighbourhood of polymer chains, which causes an increased reaction rate and at the same time an almost instantaneous reaction of the second hydrogen atom of the amino group, and thus the crosslinking of soluble polymers.

For measurements of the rate of the reaction between N-(benzyloxycarbonyl) glycine and macroporous gels based on the copolymer 2,3-epoxypropyl methacrylate–-ethylene dimethacrylate in DMF at 80°C gels of the same chemical composition but having different specific surface were prepared. The specific surface area was affected by the different ratios of cyclohexanol and 1-dodecanol in the polymerization mixture (Table II). The molar ratio of epoxy groups and N-(benzyloxycarbonyl) glycine in the initial reaction mixture was 1 : 1 (Table IV). The conversion of epoxy groups after 24, 48 and 72 h was determined from the concentration loss of glycine derivatives. The reaction rate was found to be the higher, the larger the specific surface of the gel.

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