Chemical Modifications of Insoluble Polystyrene Derivatives

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SYNOPSIS

The development of biospecific polymeric biomaterials requires new methods of chemical treatment that may be achieved whatever the involved polymeric surface without any degradation of the macromolecular structure. To check whether substitution of polymeric surfaces by epoxy groups could be a suitable way of synthesis to reach this goal, functionalization of polystyrene by epoxy groups was carried out. The respective reactions of carboxylic acids, alcohols, aldehydes, hydrochloric and sulfuric acid, and benzylamines have been extensively studied and suitable characterization has been performed on the respective polystyrene derivatives using infrared spectroscopy, elemental analysis, argentimetric titration, and acidimetric titration. In addition, a method of titration of the epoxy groups' content of insoluble functionalized polymers has been developed by the use of ^{14}C-labeled benzylamine.

INTRODUCTION

Functionalized polystyrene derivatives are numerous and various; therefore, they have been used in very different applications: first, as stationary phase for the separation of racemic mixtures of amino acids[1,2]; second, as heparinlike biomaterials[3,4]; and, more generally, for the biospecific purification of the proteins involved in the coagulation pathway[5] and in the immunitary response of the complement system[6] and of antibodies.

To synthesize biospecific polymers, varied chemical methods have been achieved.[3,7,8] Unfortunately, these drastic conditions can only be applied for the chemical modification of cross-linked polystyrene backbone or even of ethylene–styrene copolymer tubings,[4,8,9] which polymers are known to have poor mechanical properties as far as their use in the body is concerned. A lot of research have been devoted to develop functionalized biospecific polymers with suitable mechanical properties. Indeed, Cooper and Brash synthesized sulfonated polyurethanes, but they did not succeed in achieving elastomeric biomaterial.[10] It is therefore necessary to develop new ways of synthesis—consisting of chemical modifications of surfaces—in order to obtain suitable functionalized polymers with appropriate mechanical properties as well as a suitable availability of the functional groups at the surface of the biomaterial.

Indeed, these chemical groups are frequently ionic ones. During the processing, if an hydrophobic environment is prevailing around the groups because either of the hydrophobic nature of the macromolecular chain or of the solvents used for the processing, these groups might be buried. As a consequence, they might not be available at the surface, which will not be endowed with the desired biospecific properties. Therefore, these functionalizations must be performed in hydrophilic conditions, i.e., in presence of water. Moreover, such aqueous mild conditions of functionalization will prevent any degradation of the polymer chains to occur. Indeed, frequently, elastomeric polymers are easily degradated during functionalization in presence of nonaqueous solvents.

Iwakura et al.[11] and Kalal et al.[12] have shown that in anhydrous organic solvents functionalization of glycidyl methacrylate (or acrylate) copolymers by reaction of amines, carboxylic acids, phosphoric acids, alcohols, etc., onto epoxy groups could be successful. Therefore, we expected that the use of epoxy

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groups linked to a polymeric backbone could eventually be a good solution in achieving the functionalization of polymers even in aqueous conditions.

To check this possibility, we have synthesized polystyrene derivatives substituted by epoxy groups—epoxy polystyrene resin (EPR)—and extensively studied the reactions of opening of the epoxy ring in aqueous conditions with various chemical reagents in heterogeneous systems: The resulting products of the opening reactions lead to varied substituted polymers.

EXPERIMENTAL

Materials and Methods

Materials

Cross-linked polystyrene resin Bio-Beads S-X2 200-400 mesh supplied by Bio-Rad Laboratories were first washed twice and successively with 1*M* NaOH and 1*M* HCl, then washed thoroughly with distilled water and dried at 60°C under vacuum before the chemical treatment[8] to obtain polyhydroxyethylstyrene (PEHS), which is the starting material to obtain epoxidized polystyrene. All the solvents (tetrahydrofuran, dioxane, acetone, dichloromethane) were supplied by Carlo Erba and were of reagent grade or better. Epichlorahydrin, 99%; benzylamine, 99%; benzylamine hydrochloride, 99%; *N*-methyl benzylamine, 97%; 2-chloro-1-cyclohexanol, tech.; 3-chloro-1-propanol, 98%; 4-chloro-1-butanol, 97%; gluconic acid, 50% in water; D-L-lactic acid, Eur. Pharm, B.P.; 3-chloropropionic acid, 98%; mucic acid, 98%; and 3-chloropropionaldehyde diethyl acetal, tech., were purchased from Janssen Chimica, Beerse (Belgium). Tetrabutylammonium hydrogeno sulphate acid was from EGA chimie. D-Glucuronic acid, 98%; and 4-chlorophenyl acetic acid were from Aldrich Chemical Co., Milwaukee, WI. Aqueous counting scintillant liquid was from Amersham (U.S.A.). Benzylamine-ring-UL-^{14}C was supplied by Sigma Chimie, La Verpillière, France.

All the reactors used in the syntheses were commercially available classical glass ones. Infrared (IR) spectra were performed with a Perkin-Elmer FTIR 1650. Elemental analyses (EA) were performed by the Service Central d'Analyses, CNRS, Vernaison, France. Chlorine titration was performed by argentimetry (A). Acidimetric titration (AT) was performed with an automatic titrator TT100/TT300 from Tacussel Solea, Villeurbanne, France; characterization of a polystyrene derivative by AT consists in a potentiometric titration in heterogeneous phase performed by very slow addition (every 100 s) of little amounts (1.10^{-3} mL) of titrating solution to obtain the thermodynamic equilibrium between the solution and the insoluble polymer for each point at every moment. According to Ref. 4, the choice of the solvent depends on the titrated function. β counting was performed using a liquid scintillation counter 1214 Rackbeta from LKB.

Methods

Procedure I a and b: Fixation of Epoxy Groups on Polystyrene.

(a) Epoxidation on PEHS (8) —procedure Ia— was performed as follows: *Solution A* is prepared with 1 g PEHS (#5 meq), which is placed in a three-necked glass flask fitted with a reflux condenser and swollen under stirring with 30 mL of methyl ethyl ketone (MEK) for about 90 min before the addition of 2.5 mL of epichlorohydrin (#30 meq). *Solution B:* Sodium hydroxide, 7 g, is dissolved in 20 mL of distilled water to prepare a 35% aqueous solution of NaOH. *CTP:* The phase-transfer catalyst is tetrabutylammonium hydrogen sulfate acid (powder). CTP, 0.65 g, and solution B are successively added at room temperature to solution A; then the system is stirred at a temperature of 50°C for about 20 h. The suspension is then filtered at room temperature and successively washed with about 250 mL of the following different solvents: water, water–dioxane mixture (50/50), water/tetrahydrofuran (THF) mixtures (50/50 and 20/80), and pure THF before being dried at 60°C under vacuum. The characterization of epoxy polystyrene resin (EPR) was performed by EA and infrared (IR) spectroscopy.

(b) Epoxidation of PEHS by procedure Ib is a two-step procedure: *First step:* PEHS, 1 g, (#5 meq) is swollen under stirring with 30 mL of dioxane and 1 mL of epichlorohydrin (10 meq) for about 60 min at room temperature. BF_3 etherate 0.5 mL diluted in 2 mL of dioxane is added to the above mixture at room temperature, overnight 0.5 mL of pure BF_3 etherate is readded, then the system is stirred at room temperature for about 24 h. Water is slowly added to the suspension, then the resin is filtered and suspended in the different following

solvents: water/dioxane mixtures (50/50 and 20/80) and pure dioxane, before being dried at 60°C under vacuum. *Second step:* Hydroxy chlorinated derivative, 1 g, is swollen in 20 mL of methanol at room temperature before the addition of 20 mL of a molar solution of sodium methanolate in methanol. Then, the suspension is stirred and refluxed for 24 h; the resin is filtered and washed successively with water/dioxane mixtures (50/50 and 20/80), pure dioxane, and dichloromethane before being dried.

Procedure II: Opening Reaction of Epoxy Groups with Carboxylic Acids. Typical experimental conditions for the reaction of carboxylic acid with EPR (procedure II) are the following: 1 g of EPR (#1 meq) is swollen under stirring with 10 mL of distilled water and 10 mL of the aqueous acid solution prepared by addition of ~ 5 meq of acid to 10 mL of distilled water. The system is refluxed for about 20 h; then, the resin is extensively washed and dried as described above. The characterization of the resins is achieved by IR, which shows an ester band at 1680 cm^{-1}, EA, and A when chlorinated acids are used. The acids used were lactic acid, chloropropionic acid, chlorobutyric acid, chlorophenylacetic acid, gluconic acid, mucic acid, and glucuronic acid.

Procedure III: Opening Reaction of Epoxy by Hydrochloric and Sulfuric Acid. EPR, 0.5 g, is placed in 20 mL of a 50/50 dioxane–water acid mixture and refluxed for about 18 h for HCl and 6 h for SO_4H_2. Then, the suspension is filtered at room temperature and the resin is rinsed, washed, and dried as described above. The final concentrations in acid were 0.05*M* (HCl only) and 0.25*M* and 0.5*M* (HCl and SO_4H_2). Characterization was performed by IR and A.

Procedure IV: Opening Reaction of Epoxy Ring by Chlorinated Alcohols. EPR, 1 g is placed in 20 mL of H_2O/dioxane (50/50) mixture with about 10 meq of the chlorinated alcohol and refluxed for about 18–20 h. Washings and drying are performed as described above. The chlorinated alcohols used are 3-chloro-1-propanol, 4-chloro-1-butanol, and 2-chloro-1-cyclohexanol. Characterization methods of the chlorinated alcohol ether derivatives has been performed by IR spectroscopy, A, and EA.

Procedure V: Opening Reaction of Epoxy by a Chlorinated Aldehyd. Typical experimental conditions of procedure V are the following: Diethylacetal chloropropionaldehyde, 1 g, is dissolved in 20 mL of 50/50 water/dioxane mixture before the addition of 1 g of EPR. Then, the suspension is refluxed for approximately 20 h before the classical washings and drying described above are performed. The characterization involved essentially A and EA.

Procedure VI: Opening Reaction of Epoxy by Benzylamines. Reaction of benzylamine with EPR has been performed at reflux either in toluene (swelling solvent for the polymer) or in a water/dioxane mixture or even in pure water. Typical conditions of reaction (procedure VI) are the following:

(i) In anhydrous medium: EPR, 1 g, is swollen under stirring in 25 mL of toluene for 90 min before the addition of 2.5 mL of benzylamine (about 23 mmol); the suspension is refluxed at 120°C for 18–20 h. Then, the mixture is cooled at room temperature and the resin is filtered and rinsed with dichloromethane before successive washings with 250 mL of the following solutions: water, water/dioxane mixtures (80/20, 50/50, and 20/80), pure dioxane, and dichloromethane. The resin is dried under vacuum at 60°C.

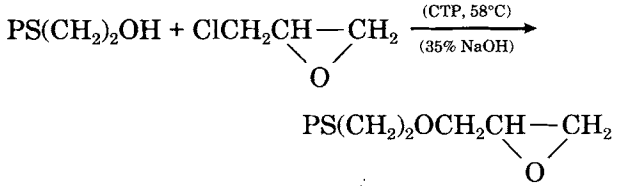
(ii) In aqueous medium: Conditions are similar to those described above (i) except that benzylamine was added as a 20% aqueous solution.

(iii) Benzylamine hydrochloride: EPR, 1 g, is placed in 50 mL of an aqueous benzylamine hydrochloride solution (~ 35 meq) with 1.5 g of sodium hydroxide (~ 35 meq); temperature, time, washings, and drying are similar to those described above. When ^{14}C-labeled benzylamine hydrochloride was used (specific activity, 1 μCie/mL, resulting in a counting of 3500–4000 dpm for 50 μL), 1 ml of the radiolabeled product solution was added to the "cold" benzylamine hydrochloride solution. In this latter case, after the reaction and the classical washings, about 5 mg of the resin is suspended in 1 mL of dichloromethane and 5 mL of scintillator liquid in propylene counting vial and counted; results will be expressed in dpm/g of resin or meq of benzylamine/g of resin. In all cases, the products were characterized by AT of the aminohydroxy derivative, EA, IR spectroscopy, and counting when the radiotracer is used.

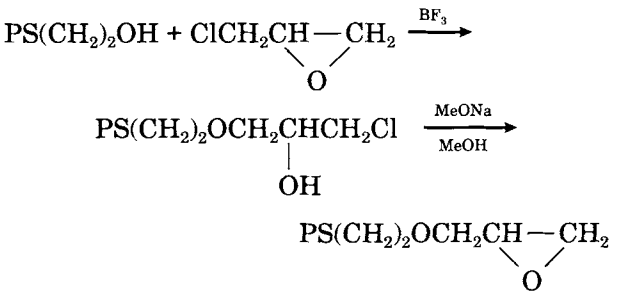
RESULTS AND DISCUSSION

Epoxidation of PEHS Resins (Procedure Ia)

The condensation of the alcohol derivative PEHS with epichlorohydrin with phase-transfer catalysis leads to the EPR:



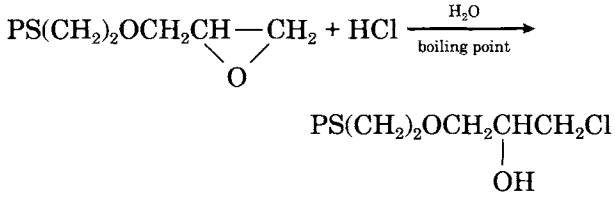
IR spectra as well as weight increases and EA of the EPR products (cf. Table I) demonstrate high yields of substitution of PEHS by epoxy groups. From a quantitative point of view, this substitution represents about 1.25 meq of epoxy groups by gram of EPR; a better substitution rate (1.5 meq/g, cf. Table I) can be obtained using a two-step procedure (procedure Ib) that consists in the reaction of epichlorohydrin in presence of a Lewis acid in anhydrous medium on PEHS, leading to the chlorinated alcohol derivative; in the second step, the latter compound is cyclized by sodium methylate in methanol according to



It is worth noting that procedure Ia is easier and more reproducible than is procedure Ib. About 20 IR spectra of differents EPR products obtained following procedure I were performed and systematically compared to those of PEHS; whereas the PEHS spectrum showed the typical OH frequency centered around 3360–3380 cm^{-1}, the EPR spectrum showed reproducibly a shift of the OH frequency to 3450 cm^{-1} and parallelly exhibited the typical epoxy absorption at 1250 and 905 cm^{-1}. On the other hand, concerning the ratio of the intensities of the two bands at 1420–1450 cm^{-1} of PEHS, the lower the ratio, the better the yield.

Reaction of Hydrochloric and Sulfuric Acids

Hydrochloric acid was found to be strongly reactive toward epoxy groups: Indeed, depending on its concentration (see Table II), it opens rapidly and quantitatively epoxy groups, leading to the corresponding chlorinated alcohol derivative according to



Indeed, reaction of EPR with a 0.25M solution of HCl results in the opening of the epoxy rings leading to the chlorinated compound. For lower concentrations (0.05M), the dialcohol derivative is obtained. Oppositely, sulfuric acid was found to be less reactive: Indeed, in the same conditions (0.25 and 0.5M), the only product of the reaction is the hydrolyzed epoxy, i.e., the dialcohol (see Table II):

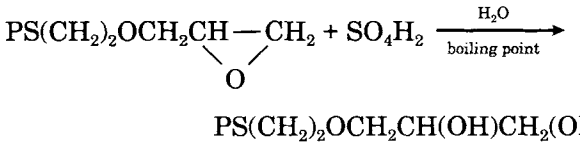


Table I Typical Results of EA for PEHS and for EPR

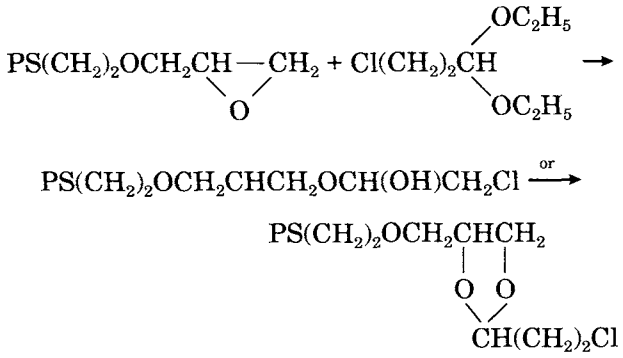
Nature of the resin	Elemental analysis (% of) C	H	O	N	Epoxy Groups Content (meq/g)
PEHS theory	81	8	10.8		—
PEHS	76.8	7.4	10.6	0.46	—
EPR theory	76.5	7.8	15.7		—
EPR procedure I	78.08	7.59	12.67	0.47	1.25
EPR procedure II	74.5	7.6	13.4	0.4	1.5

Table II Typical Results of Reaction of HCl and H_2SO_4 on EPR

Acid	Concentration (M)	EA on Cl (meq/g)	Reaction Products Identified by IR
HCl	0.05	0.5	Chlorinated and dialcohol derivative
HCl	0.25	1.25	Totally chlorinated
H_2SO_4	0.25	—	Dialcohol derivative
HCl	0.5	1.4	Totally chlorinated
H_2SO_4	0.5	—	Dialcohol derivative

Reaction of Aldehyde on Epoxy Groups

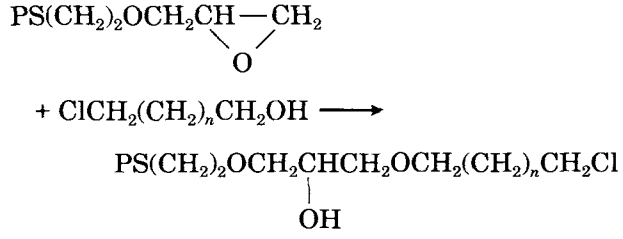
The reaction of a chlorinated aldehyde (chloropropionaldehyde) on the epoxidized polymer gives the corresponding mono- or diacetal:



The characterization of the product was performed by EA, A, and IR. EA and A gave essentially the same results (1.25 meq/g of Cl), leading to the conclusion that the reaction of chloropropionaldehyde on the epoxy resin is total.

Reaction of Chlorinated Alcohols on EPR

The opening reactions of epoxy with chlorinated alcohols (procedure IV) lead to the obtention of the alcohol ether derivatives:



The chlorinated alcohols used were a primary (3-chloro-1-propanol, 4-chloro-1-butanol) or secondary (2-chloro-1-cyclohexanol) one and the products were characterized by EA, A, and IR.

The results of chlorine (Table III) are similar for one alcohol and for both methods (EA and A), and the same is true whatever the alcohol involved: Indeed (cf. Table III), the small differences observed are not significant. The comparison of the IR spectra of one EPR and of the three alcohol ether derivatives show the systematic disappearance of the epoxy bands parallelly to the appearance of a substitution band around 700 cm^{-1}, which can be attributed to C—Cl.

No significative difference could be noted either on the IR spectra of the three reaction products or in the chlorine titration; therefore, we conclude that there is no difference in the reactivities of the three chlorinated primary or secondary alcohols.

Reaction of Carboxylic Acids on EPR

The opening reaction of epoxy groups by the following acids: lactic, chloropropionic, chlorophenylacetic, gluconic, mucic, and glucuronic, has been performed according to procedure IV described above.

Characterization of the products was performed by IR spectroscopy. In case of the lactic, chloropropionic, and chlorophenylacetic acids, the IR spectra

Table III Compared Reactivities of Different Chlorinated Alcohols on EPR: Typical Results

	Characterization Method	
Reagent	EA on Cl (meq/g)	A of Cl (meq/g)
3-Chloro-1-propanol	1.3	1.1
4-Chloro-1-butanol	1.2	1.1
2-Chloro-1-cyclohexanol	1.25	1.1

showed a strong characteristic ester band at 1730 cm^{-1}, which demonstrates that the acids react with the epoxy groups. In contrast, no ester band could be observed in the product of the reaction of EPR with gluconic or mucic acid; moreover, their IR spectra are identical to those obtained when EPR are hydrolyzed in the presence of an aqueous sulfuric acid solution (see above), demonstrating that gluconic and mucic acids behave like sulfuric acid. In the case of the glucuronic acid, reaction with EPR, the IR spectrum of the product is almost identical to that of EPR, demonstrating that no reaction occurred. A and EA have been performed on the products in the case of chlorinated acid and gave essentially the same results (Table IV).

The above-mentioned results can be summarized by the following reactional schemes:

(a) In the case of lactic, chloropropionic, and chlorophenylacetic acids, the reaction is the opening of the epoxy ring followed by the formation of an alcohol ester derivative:

$$PS(CH_2)_2OCH_2CH\!-\!CH_2 + RCOOH \longrightarrow PS(CH_2)_2OCH_2CH(OH)CH_2OCOR$$

(b) In the case of gluconic and mucic acids, the reaction consists in the hydrolysis of the epoxy group:

$$PS(CH_2)_2OCH_2CH\!-\!CH_2 + RCOOH \longrightarrow PS(CH_2)_2OCH_2CH(OH)CH_2(OH)$$

(c) In the case of glucuronic acid, no reaction occurs.

Moreover, when EPR reacted, the reactivities of the acids decrease in the following order: lactic, chloropropionic = chlorophenylacetic, gluconic, mucic. The change in the reactivities of the acids correlates with their pK: the lower the pK, the higher is the yield of the reaction, except for glucuronic acid. In the latter case, it is possible that the complex structure of the acid is responsible for the observed results.

Opening Reaction of Epoxy Groups by Benzylamines

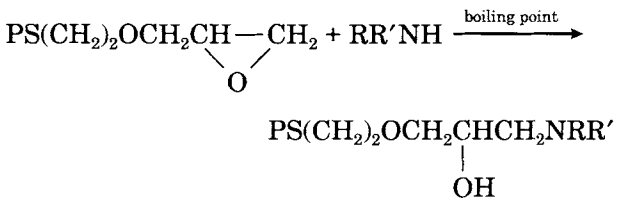
The amino hydroxy polystyrene (PS) derivative is obtained opening the oxiranne ring of EPR by a primary amine (benzylamine, procedure VI) according to the following scheme:

$$PS(CH_2)_2OCH_2CH\!-\!CH_2 + RNH_2 \xrightarrow{\text{boiling point}} PS(CH_2)_2OCH_2CH(OH)CH_2NHR$$

Table IV Typical Results of Reactivities of Different Acids on EPR

Reagent	Characterization Method		
	EA on Cl (meq/g)	A of Cl (meq/g)	IR Ester Band at 1730 cm^{-1}
Lactic acid	—	—	+++
Chloropropionic acid	0.7	0.6	+++
Chlorophenyl acetic acid	0.76	0.65	+++
Gluconic acid	—	—	––– Dialcohol derivative
Mucic acid	—	—	––– Dialcohol derivative
Glucuronic acid	—	—	––– Epoxy groups intact

The same but secondary amine (methylbenzylamine) has also been shown to react with EPR in the same conditions as those described procedure VI according to



Characterization of the products has been performed by four methods and the results are presented in Table V and by the following:

(a) IR spectroscopy demonstrates the opening of epoxy groups, resulting in the addition of benzylamine; the epoxy bands at 1250 and 905 cm^{-1} disappeared, whereas, simultaneously, the characteristic amino substitution band at 743 cm^{-1} appeared.

(b) AT of the aminohydroxy PS derivative in methanol allowed the determination of the amount of secondary amine linked to the polymer backbone (1.2 meq/g). A typical titration curve is presented Figure 1: It shows the characteristic plateau at pH 8.25. When methylbenzylamine was used, the AT of the tertiary amine linked to the macromolecular chain gave essentially the same result.

(c) EA of the samples based on the nitrogen content gives a mean of N equal to 1.42 meq/g.

(d) Determination of the yield of the reaction of benzylamine with EPR was also achieved by use of ^{14}C-labeled benzylamine and gave yield of 1.3 meq/g of benzylamine linked to the polymer chain.

All the methods of characterization used gave essentially the same results. Indeed, when the IR spectrum showed that the reaction of the epoxy groups was total, AT, EA, and β counting gave an average nitrogen content of the aminohydroxy PS derivative of 1.3 ± 0.1 meq/g. The small differences between the results given by each of the three methods are in the range of accuracy of each method.

It is noticeable that the latter figure is in good agreement with the above-mentioned results regarding the content of epoxy groups in EPR (1.25 meq/g). Moreover, these results show that the reaction of primary aminelike benzylamine as well as secondary aminelike methyl benzylamine is quantitative. Therefore, it is possible to assess the content of epoxy groups in functionalized polymers by use of ^{14}C-labeled benzylamine and β counting. This method is general and highly sensitive. Indeed, the limit of sensitivity of the method was found to be along the order of 1 μeq/g with an accuracy of about 10% in case of epoxidized polymers kindly supplied by G. Wajs from Essilor, France.

CONCLUSIONS

Epoxidized polystyrene resins with high yields of substitution in epoxy groups were synthesized. This allowed an extensive study of the reactivity of the epoxy rings in aqueous medium when linked to the macromolecular chain in an hydrophobic environment. Reactions were performed in mild conditions that allow similar chemical modification of polymers sensitive to more drastic conditions of reaction. In these conditions, it appears that

(a) The reaction of acids like hydrochloric acid, lactic acid, chloropropionic acid, and chlorophenylacetic acid on EPR resulted in the for-

Table V Reaction of Benzylamines on EPR: Comparison of the Characterization Methods

	Characterization Method			
Reagent	EA on Cl (meq/g)	A of Cl (meq/g)	β Counting	IR (743 cm^{-1})
Benzyl amine	1.42	1.23	—	++
Methyl benzylamine	1.54	1.4	—	+++
HCl, ^{14}C-benzylamine	—	1.2	1.3	—

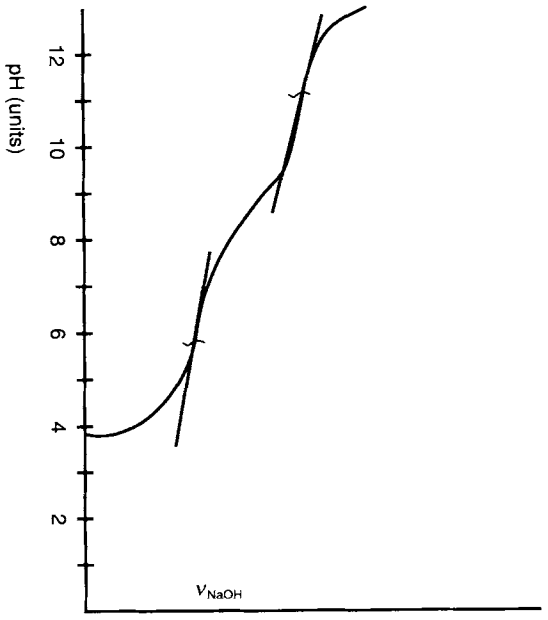


Figure 1 Titration curve of the hydroxyamino PS derivative resulting from the reaction of benzylamine with EPR.

mation of an alcohol ester; in contrast, SO_4H_2 resulted in the hydrolysis of the epoxy ring to form the diol. It is interesting to note that all these reactions of acids on epoxy groups were performed in water and led to conversion rates as high as 70%. These results were unexpected for several reasons: First, Kalal et al.[12] described the reaction of acids on epoxy rings and showed that conversion could reach 20% at best, i.e., in anhydrous medium, and fall to about 5% in the presence of small amounts of water; second, even if water is not the solvent required for the swelling of a macromolecular structure like cross-linked polystyrene, reactions proved to occur, leading to high rates of conversion.

(b) The reaction of primary or secondary alcohol on EPR gave a 80% yield of the alcohol ether derivative.

(c) The reaction of aldehyde on EPR is strong and total and leads to the formation of a mono- or diacetal with no possibility of distinguishing between the two species.

(d) The reaction of benzylamine on EPR is total; this allows the setup of a new method of determination of epoxy content that is very sensitive and can be applied to any insoluble material even if its epoxy content is very low, along the order of 1 microequivalent by gram of product. Therefore, the characterization of the epoxy group content of any epoxidized material can be achieved following either the amino titration method or the β titration method, which is very attractive in the case of weakly epoxidized materials. Moreover, it is of particular interest that whatever the nature of the solvent from toluene to water, the reaction is quantitative.

(e) Surprisingly, gluconic and mucic acids that possess both alcohol and carboxylic functions behave differently; indeed, the opening of the oxiranne cycle resulted in no formation of either esters or ethers. In this regard, they are similar to SO_4H_2. Moreover, glucuronic acid, which has three functions, namely, aldehyde, acid, and alcohol, does not react at all in these mild conditions.

In conclusion, this study provides useful tools for the heterogeneous functionalization of elastomeric polymers that are actually under study.

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