Preparation of Chloromethylated and Aminated Gel-Type Poly(styrene-*co*-divinylbenzene) Microparticles with Controlled Degree of Functionalization

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ABSTRACT: The possibility of adjusting the degree of hydrophilic functionalization in polymeric microparticles with a hydrophobic skeleton makes it possible to obtain adsorbents and catalyst microparticles that may show better performance. In this regard, in this study, gel-type poly(styrene-*co*-divinyl benzene) microparticles were chloromethylated and subsequently aminated, and the quantitative effect of the chloromethylation reaction conditions on the final degree of functionalization achieved were examined. In the chloromethylation route, methylal, thionyl chloride, and a Friedel–Craft catalyst were used. From the experimental results, two models were obtained by multiple linear regression relating the chloromethylation conditions to the anion-exchange capacity (AEC) achieved and to the replaceable chlorine content, according to which the achievement of a high degree of useful functionalization within the microparticles entailed chloromethylation with low methylal/polymer molar ratios and high thionyl chloride/polymer molar ratios, relatively high temperatures, and short reaction times; all of these values were within the ranges used in this study. Additionally, we found that the highest values of AEC could be reached with a methylal/thionyl chloride molar ratio close to unity. The models obtained could be useful for the synthesis of microparticles with required degrees of functionalization, that is, with the chosen hydrophilicity/hydrophobicity ratio. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 130: 4054–4065, 2013

INTRODUCTION

Adsorption on solid microparticles and ion exchange are operations commonly used for the separation and purification of the components of mixtures. These separations are driven by favored interactions between the target substances and the solid surfaces, whose nature is usually of hydrophobic or hydrophilic type. Thus, in the case of anion-exchange chromatography, which is the most common procedure for the separation and purification of biomolecules,[1–4] the attractive forces are electrostatic, that is, forces that can be included within hydrophilic interactions. However, in some cases, the adsorbent/adsorbate interactions are more complex because both hydrophilic and hydrophobic interactions can take place. As an example, polystyrene-based anion-exchange resins have positively charged quaternary ammonium groups, whose charge is balanced by anions that can be exchanged. These charged functional groups confer hydrophilicity to the resins, although in this particular case, because the amino groups are attached to a polymeric backbone that has hydrophobic characteristics, the existence of

hydrophobic interactions is also possible. In some applications, this duality of forces can be a drawback, but in other cases, it must be regarded as an advantage because, when the density of hydrophilic functional groups is adjusted, adsorbent materials with controlled hydrophilic and hydrophobic characteristics can be prepared. In this way, the viability of the modulation of the density of hydrophobic and hydrophilic areas in some types of solid microparticles opens the feasibility of the preparation of adsorbents with much more selective adsorption properties than when only hydrophilic or hydrophobic forces are present, in a similar way to what is achieved with adsorbents that are suitable for affinity chromatography. The importance of the hydrophobicity/hydrophilicity ratio should not be neglected because it can be exploited to improve the operational results[5–8] of ion-exchange resins across their wide range of applications: from the exchange of anions to their use as catalysts.[6,9–13] However, to the best of our knowledge to date, no systematic methods of regulating their hydrophobicity/hydrophilicity ratios have been reported.

In this regard, it seems clear that the most direct way to achieve the knowledge or skills needed to regulate the density of functional groups in ion-exchanging microparticles would be to carry out a systematic study to ascertain the effects of variations in the synthesis parameters on the final degree of functionalization obtained. The aim of this study was to establish a mathematical model that would relate the final degree of functionalization to the operation conditions in the synthesis. This model would permit the synthesis of resins with predetermined adsorption properties and hence contribute to a reduction in the costs of separation and purification in certain processes.[14]

In the synthesis process of anion-exchange resins based on polystyrene, the main industrial process used in their manufacture consists of the amination of chloromethylated polystyrene based microparticles,[11,15] with the chloromethylation of the benzene rings being the key step in this process[16] because the degree of availability of chlorine atoms to be replaced by new functional groups depends on the type of the chloromethylation procedure chosen and, within each procedure, on the reaction conditions. In this regard, the importance of a knowledge of the effects of the chloromethylation reaction conditions on the replaceability of chlorine atoms by other functional groups must be emphasized because, apart from their use as anion-exchanger precursors, chloromethyl-substituted styrene-co-divinylbenzene copolymers are key in many applications, such as in solid-phase peptide synthesis,[17] precursors for protein adsorbents,[18] and precursors of catalysts.[19] Thus, in the manufacture of anion-exchange resins, there is an intermediate with a large number of applications, which has functional groups whose density also can be adjusted, and as a result, the hydrophobicity of its polymeric backbone can be modulated. Accordingly, again in this case, it is worth noting that the establishment of mathematical models between the reaction conditions and the degree of chloromethylation attained could aid in the modulation of the properties of the polymeric matrix, and in this way, polymeric microparticles could be tailored for subsequent applications.

Furthermore, with the synthesis process, the traditional route used to achieve the chloromethylation of polystyrene-based microparticles involves the direct use of potentially carcinogenic substances such as chloromethyl methyl ether (CMME).[20] Another alternative chloromethylation route is that proposed by Galeazzi,[21] in which methylal is used as a swelling and methylating agent, and thionyl chloride is used as a chlorinating agent in the presence of Lewis acids as Friedel–Craft catalysts. In Appendix A, a more detailed explanation of the Galeazzi procedure is given. Because of the side reactions involved in the cloromethylation of poly(styrene-co-divinylbenzene) [P(St–DVB)], our aim was to explore the efficiency of the process involving chloromethylation through control of the chloromethylation conditions used to attain microparticles with functional groups that would be of use for the desired application. In particular, we focused our attention on the final functionalization with amino groups to transform the chloromethylated microparticles into anion-exchange resins (Scheme 4, shown later).

As stated previously, taking into account that the final aim of this study was to find a mathematical relationship between the operating conditions of the synthesis in both the chloromethylation and the amination processes and the degree of functionalization attained in each case, in this study, we carried out the manufacture of anion-exchange resins by chloromethylation and the further amination of P(St–DVB) microparticles, and the accomplishment of the main aim was approached by means of the determination by multiple linear regression of the quantitative influence of the experimental conditions used in the chloromethylation of polystyrene-based microparticles previously obtained in our laboratory[22,23] on the anion-exchange capacity (AEC) of the solid. Furthermore, the efficiency of the amination (Y_{AM}) was tested by comparison of the values of the chlorine content derived from elemental microanalysis and those calculated from the values of AEC. Additionally, the morphology and topography of the microparticles were examined by light microscopy and scanning electron microscopy (SEM) to check that those characteristics were maintained throughout the functionalization process. Finally, Fourier transform infrared (FTIR) spectroscopy was used to monitor the reactions occurring in the microparticles during the manufacturing process of the gel-type anion-exchange resins.

From the experimental results, two models were obtained by multiple linear regression that related the chloromethylation conditions to the achieved AEC and to the replaceable chlorine content, according to which the achievement of a high degree of useful functionalization within the microparticles entailed the use of chloromethylation with low methylal/polymer molar ratios (Met factor) and high thionyl chloride/polymer molar ratios ($SOCl_2$ factor), relatively high temperatures, and short reaction times, with all these values within the ranges used in this studies. Additionally, we found that the highest values of the AEC could be reached with a methylal/thionyl chloride molar ratio close to unity.

These models obtained could be useful for the synthesis of microparticles with the required degrees of functionalization, that is, with the chosen hydrophilicity/hydrophobicity ratio.

EXPERIMENTAL

The P(St–DVB) microparticles used for functionalization were obtained in our laboratory through a suspension polymerization technique.[22,23] In fact, the microparticles used in this study were those obtained in ref. [22]. In this section, we describe the materials and methods used for the manufacture of the anion-exchange resins based on those P(St–DVB) microparticles.

Chloromethylation of the P(St–DVB) Microparticles

Materials. The materials used in the chloromethylation of the P(St–DVB) microparticles were methylal (99%) and zinc chloride (≥98%), both supplied by Aldrich (Madrid, Spain), and thionyl chloride (purum), obtained from Fluka (St. Gallen, Switzerland). All of these materials were used as received. Deionized water and ethanol (96%, CUVE, Cordoba, Spain) were also used in the process.

Experimental Procedure. The chloromethylation of the microparticles was carried out with methylal as a methylating agent

and thionyl chloride as a chlorinating agent in the presence of zinc chloride as a catalyst. The microparticle functionalization was carried out in a 250-mL, three-necked, round-bottom glass flask equipped with a reflux condenser and a thermometer. Internal stirring was accomplished with a magnetic stirrer. First, P(St–DVB) microparticles (2.5 g) were dispersed in a given volume of methylal inside the reactor at a fixed temperature, depending on the experiment. After 30 min, a solution of zinc chloride in 10 mL of methylal, whose concentration also depended on the experiment, was poured into the flask, and finally, thionyl chloride was added. The reaction time (which was predetermined for each experiment) was measured from the moment at which all the thionyl chloride had been poured into the reactor. Once the preset time of the reaction was reached, the microparticles were washed with water and ethanol and then dried in a vacuum oven overnight. There was no evidence of particle attrition either under light or SEM.

Amination of the Chloromethylated P(St–DVB) Microparticles. Materials. The trimethylamine (TMA; ~45% solution in water) used in the amination of the chloromethylated P(St–DVB) microparticles was supplied by Fluka and was used as received. Deionized water was used to wash the particles thoroughly after the amination.

Experimental Procedure. After the chloromethylated microparticles were dried, the aqueous solution of TMA (20 mL) was poured into a beaker over the chloromethylated microparticles (1 g) to induce the replacement of the chlorine atoms by quaternary ammonium groups and transform the microparticles into anion-exchange resins. The amination was performed at room temperature and under magnetic stirring for 48 h. Then, the microparticles were washed thoroughly with water. These conditions were used because they proved to be adequate for the maximum AEC of all of the solids obtained to be achieved.

Characterization of the Functionalized Microparticles
Determination of the Chlorine Content. To quantify the chlorine content of the chloromethylated microparticles, that is, the percentage by weight of chlorine within the chloromethylated solid (%Cl$_{MA}$), elemental microanalysis was performed with the Schöninger method.[24] This method consists of burning out a known amount of the chlorinated sample in a closed flask and then collecting the combustion gases in a basic solution to determine the chlorine concentration by potentiometric titration with silver nitrate.

Measurement of AEC. To measure AEC of the resins, a standard method was used[25] and is summarized as follows. The aminated microparticles were placed in a column and were first treated with an excess amount of 1N HCl solution to ensure the complete loading of the resins in the chloride form. The amount of HCl solution used was more than 20 column volumes. After this, the Cl-form aminated microparticles were thoroughly washed with ethanol until the effluent was neutral to eliminate the excess hydrochloric acid. After the neutralization of the resins, a known amount of wet microparticles was poured into a column and leached with a 4% Na$_2$SO$_4$ solution to replace the Cl$^-$ ions in the resins with SO$_4^{2-}$ ions. The effluent Na$_2$SO$_4$ solution was collected, and the chloride ions

removed from the resins were titrated with a 0.01M AgNO$_3$ solution with potassium chromate as an indicator.[26] The dry weight fraction of the neutralized Cl-form resins was determined from the weight loss of the microparticle samples treated at 110°C for 16 h in an oven. In this way, the AEC value was calculated as the equivalents of chloride ion titrated with AgNO$_3$ per gram of dried resin.

IR Spectra. To investigate the transformations occurring in the resins in each step of the manufacture of the anion exchangers, FTIR spectra of KBr pellets of carefully ground polymer beads were recorded on a PerkinElmer 1600 series spectrophotometer. The assignments of the absorptions bands were made with standard sources.[27,28]

Light Microscopy and SEM. The morphology and topography of the resins before and after the functionalization processes were studied by light microscopy with a ZUZI 172 light microscope, and their surface topography was investigated by SEM with a Zeiss DSM 940 microscope.

Design of the Experiments
The research was planned through a factorial design of experiments.[29,30] This technique was chosen as a tool for the determination of the existence of cause–effect relationships. To apply this methodology, a sequence of steps had to be followed.

Problem Identification. As pointed out before, chloromethylated P(St–DVB) is an intermediate of great value for many applications, and the regulation of the density of functionalization may be a very useful tool in optimizing these applications. However, the chloromethylation procedure entails the existence of a series of side reactions that lead to a decrease in the number of chlorine atoms that can be substituted by suitable functional groups that are able to afford the microparticles their intended final usefulness. With this problem taken into account, it appeared highly desirable to investigate how to optimize the manufacturing process of the chloromethylated P(St–DVB) microparticles so that most of the chlorine atoms could be replaced by any other functional group. However, because the achievement of this overall goal was very difficult, it seemed instead more practical to attempt optimization with respect to a particular final functionalization, that is, with respect to the introduction of functional groups of a given size and reactivity. In this regard, optimization could be approached through the quantification of the influence of the reaction conditions on the final degree of functionalization of the resins. Because our aim in this study was to prepare anion-exchange resins, the final degree of functionalization studied was AEC, which was also a measurement of the availability of chlorine atoms within the polymeric structure to be replaced by quaternary ammonium groups.

Factor Identification. Because the process of manufacturing anion-exchange resins based on P(St–DVB) microparticles is mainly divided into two steps, chlorination and amination, in principle, the factors whose influence are to be studied should be selected from both processes. However, because the reaction conditions to achieve the maximum AEC during the amination are simply a matter of temperature and time in the presence of

Table I. Factor Levels of the Experiments to Manufacture Gel-Type Anion-Exchange Resins

Experiment Nomenclature		Factor level									
		Met		SOCl₂		ZnCl₂		T (°C)		Time (h)	
Chloromethylated	Aminated	Real value[a]	Coded value	Real value[a]	Coded value	Real value[a]	Coded value	Real value	Coded value	Real value	Coded value
CM-1	AM-1	9.4	−1	7	−1	0.3	−1	32	−1	8	+1
CM-2	AM-2	14.4	+1	7	−1	0.3	−1	32	−1	6	−1
CM-3	AM-3	9.4	−1	11.1	+1	0.3	−1	32	−1	6	−1
CM-4	AM-4	14.4	+1	11.1	+1	0.3	−1	32	−1	8	+1
CM-5	AM-5	9.4	−1	7	−1	0.5	+1	32	−1	6	−1
CM-6	AM-6	14.4	+1	7	−1	0.5	+1	32	−1	8	+1
CM-7	AM-7	9.4	−1	11.1	+1	0.5	+1	32	−1	8	+1
CM-8	AM-8	14.4	+1	11.1	+1	0.5	+1	32	−1	6	−1
CM-9	AM-9	9.4	−1	7	−1	0.3	−1	38	+1	6	−1
CM-10	AM-10	14.4	+1	7	−1	0.3	−1	38	+1	8	+1
CM-11	AM-11	9.4	−1	11.1	+1	0.3	−1	38	+1	8	+1
CM-12	AM-12	14.4	+1	11.1	+1	0.3	−1	38	+1	6	−1
CM-13	AM-13	9.4	−1	7	−1	0.5	+1	38	+1	8	+1
CM-14	AM-14	14.4	+1	7	−1	0.5	+1	38	+1	6	−1
CM-15	AM-15	9.4	−1	11.1	+1	0.5	+1	38	+1	6	−1
CM-16	AM-16	14.4	+1	11.1	+1	0.5	+1	38	+1	8	+1

[a] mol (mol of polymer)⁻¹.

an excess of amines,[31] the key step in the global process is chloromethylation.

Consequently, the factors studied here were the operational conditions in the chloromethylation process related to the degree of chlorination and hence the AEC achieved.[32–35] Specifically, the factors whose influence was studied were as follows:

- Molar ratio of methylal to polymer (Met): Methylal participated in the reaction as a methylating agent and also swelled the microparticles, favoring larger distances between aromatic rings and thus preventing the formation of methylene bridges.
- Molar ratio of Thionyl Chloride to polymer (SOCl₂): Thionyl chloride is the substance that provided the chlorine atoms; hence, its importance was fundamental.
- Molar ratio of zinc chloride to polymer (ZnCl₂): Zinc chloride was chosen to minimize the formation of methylene bridges, because this Friedel–Craft catalyst is a weak Lewis acid.[11,36] The proportion of this substance was related to that of the methylating agent and the chlorinating agent, but it did not have an important influence beyond a certain proportion.[35]
- Temperature of the reaction (T): This factor was studied because its influence was very important in the chemical reaction and may have had a significant effect on the performance of the different reactions occurring in the chloromethylation process.
- Time of the reaction (Time): Because there were several side reactions in this process, it was not certain that longer reaction times would lead to microparticles with a higher degree of functionalization.

Level Identification. After carrying out some exploratory experiments, we decided to study the factors within the range of values summarized in Table I.

Response Identification. To attain the objective of this research, it was necessary to determine the quantitative effect of the experimental conditions of the chloromethylation of the P(St–DVB) microparticles on AEC of the anion exchangers obtained after their subsequent amination. Therefore, AEC was the main response to be measured. Moreover, because the manufacturing of anion-exchange resins based on P(St–DVB) consists of two processes, chloromethylation and amination, the degree of chlorination of the chloromethylated solid was also quantified by elemental microanalysis as %Cl$_{MA}$. The determination of these two values enabled the estimation of the efficiency of chloromethylation and also the assessment of the proportion of chlorine atoms transformed into quaternary ammonium groups after amination. Thus, the chloromethylation efficiency (Y_{CM}; %), defined as the percentage of the aromatic rings of the polymer that are chloromethylated, was calculated by eq. (1):

$$Y_{CM} = \frac{\frac{\%Cl_{MA}}{100} \times \frac{M_{wP(St-DVB)}}{M_{wCl}}}{1 - \frac{\%Cl_{MA}}{100} \times \frac{M_{wPCM}}{M_{wCl}} \left(1 - \frac{M_{wP(St-DVB)}}{M_{wPCM}}\right)} \times 100 \quad (1)$$

where M_{wCl} is the atomic weight of the chlorine atom, $M_{wP(St-DVB)}$ is the molecular weight of the structural unit of crosslinking of the P(St–DVB) polymer with 5.5% divinylbenzene (DVB), and M_{wPCM} is the molecular weight of the structural unit of the chloromethylated P(St–DVB) in which each aromatic ring is functionalized.

Moreover, because the substitutable chlorine content in the chloromethylated solid could be calculated from the AEC values, it was possible to determine the efficiency of the replacement of chlorine atoms by quaternary ammonium groups in the amination step by comparison of the chlorine contents obtained in both ways. The calculation of the substitutable chlorine content in the chloromethylated solid could be achieved through the following expression:

$$\%Cl_{AEC} = \frac{\frac{AEC}{1000} M_{wCl}}{1 - \frac{AEC}{1000} M_{wN(CH_3)_3}} \times 100 \qquad (2)$$

where $\%Cl_{AEC}$ represents the percentage by weight of the chloromethylated microparticles, which corresponds to the chlorine that is replaceable by amino groups; AEC is the anion-exchange capacity (mequiv/g); and $M_{wN(CH_3)_3}$ is the molecular weight of the TMA group.

Thus, $Y_{AM}(\%)$, which is the proportion of substitutable chlorine atoms to the total chlorine atoms included in the polymeric network, could be calculated with eq. (3):

$$Y_{AM} = \frac{\%Cl_{AEC}}{\%Cl_{MA}} \times 100 \qquad (3)$$

Planning of the Experiments. The research was planned through an unreplicated fractional factorial design of experiment of the 2^{5-1} type, where 2 is the number levels of each factor investigated, 5 is the number of factors investigated, and 5-1 indicates that it was a fractional factorial design and only 2^4 experiments have been performed instead of the 2^5 experiments of a full factorial design. The factorial design of experiments carried out is collected in Table I. The experimental design chosen did not leave any degrees of freedom to estimate the experimental error because it was an unreplicated design. Moreover, the experimental error could not be assumed as the variability of the higher order interactions because this was a fractional design with a resolution V; that is, the three-factor and higher interactions were aliased with the main effects of the factors and two-factor interactions. Therefore, an alternative methodology was used to estimate the experimental error, as shown in the Response Analysis section.

RESULTS AND DISCUSSION

Light Microscopy and SEM Analyses
The morphology of the anion-exchange resins was studied by light microscopy, and the preservation of the spherical morphology of the microparticles after their chloromethylation and subsequent amination is shown in Figure 1(a). In addition, although the color of the microparticles turned orange after the transformation process, the microparticles were transparent; this indicated that their functionalization to transform them into anion-exchange resins did not modify their texture, which remained gelatinous throughout the process. Moreover, with the scale bar, it was possible to estimate the size of the microparticles, with most of them being smaller than 100 μm. The topography of the resins was inspected by SEM. Figure 1(b) shows the aminated microparticles of experiment AM-11; this corroborated the conclusions drawn from the light microscopy analysis. In Figure 1(b,c), some irregularities are evident on the
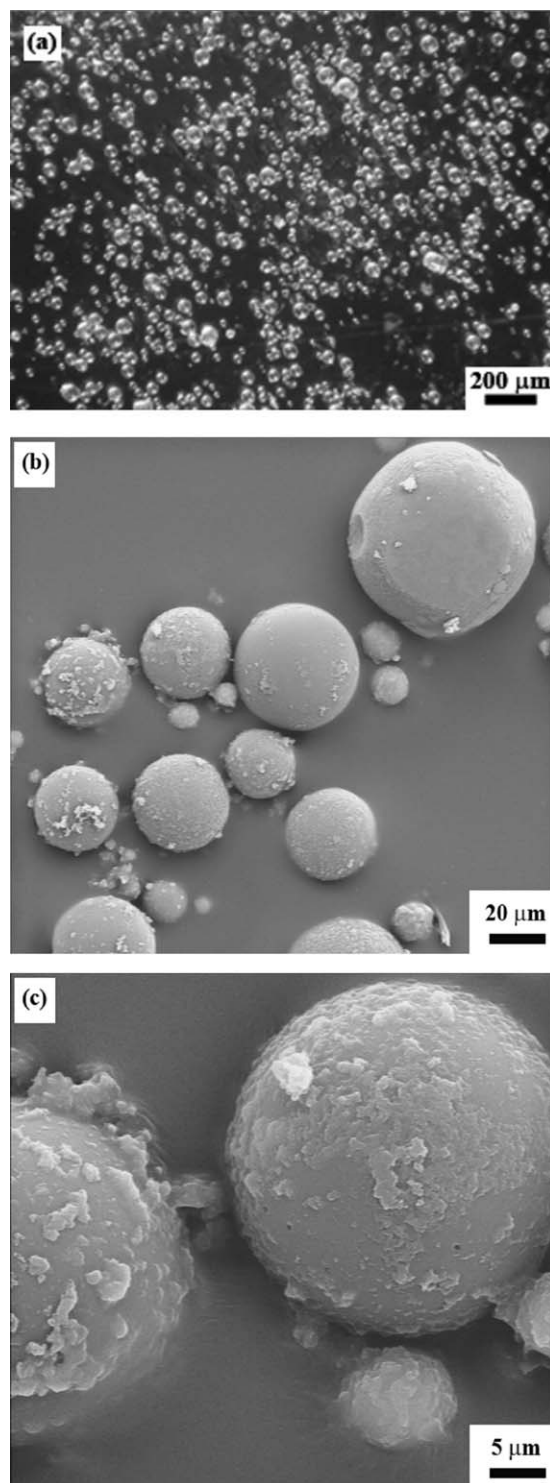
Figure 1. Microphotographs of gel-type polystyrene-based anion-exchange resins obtained with (a) light microscopy and (b,c) with SEM (experiment AM-11).

surface of the microparticles; these were probably caused by the persistent collisions between particles of very different sizes in the advanced stages of the polymerization process, in which particle coalescence did not occur, whereas transient superficial fusions followed by new separations were observed.[22]
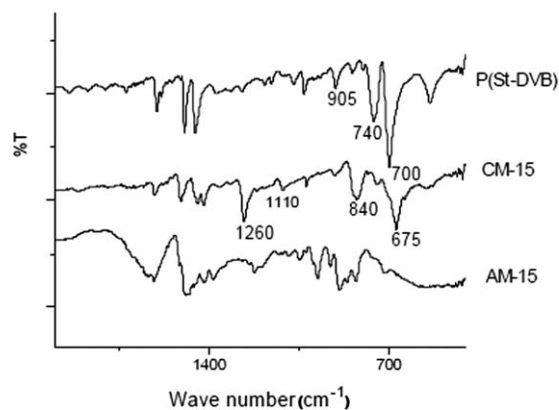
Figure 2. IR spectra of the P(St–DVB) microparticles and their chloromethylated (CM-15) and aminated (AM-15) derivatives.

FTIR Analyses

The IR spectra of the microparticles of the precursor polymer, P(St–DVB), and after the CM-15 and AM-15 experiments are shown in Figure 2, where %T represents the percentage of transmittance. In the spectrum of P(St–DVB), a characteristic absorption band of the monosubstituted vinyl group was noted (900 cm^{-1}). The intensity of this band was reduced in favor of the appearance of a characteristic peak of an ether bond at 1110 cm^{-1} in the spectrum of the chloromethylated microparticles. According to the literature,[16,37] this peak in the chloromethylated solid indicated that CMME was formed in the chloromethylation medium because this substance would produce the chlorinated ether group in the P(St–DVB) microparticles by reaction with a vinyl group during the chloromethylation process. Moreover, the spectrum of these P(St–DVB) microparticles also showed peaks that corresponded to unsubstituted styryl residues (740 and 700 cm^{-1}). After chloromethylation, the peaks of the unsubstituted styryl residues disappeared, and a characteristic band of para-substituted aromatic ring residues appeared at 840 cm^{-1}.[28] The appearance of this peak at 840 cm^{-1} indicated that the inclusion of chloromethyl groups into the aromatic rings took place at the *para* positions. This result was consistent with the rules concerning the effects of the substituents on the regioselectivity of electrophilic aromatic substitution. In addition, the IR spectrum of the chloromethylated microparticles showed two additional peaks characteristic of the vibrations of the C—Cl bond in the benzyl chloride group at 1260 and 675 cm^{-1} [37], which disappeared completely after amination. Finally, it was difficult to extract any information about the aminated microparticles from the IR spectrum, apart from the disappearance of the peaks at 1260 and 675 cm^{-1}.

Degree of Functionalization

After carrying out the functionalization experiments, we determined the degree of functionalization of the solids in two ways, as described later.

Degree of Chloromethylation. The degree of chloromethylation was estimated by determination of %Cl$_{MA}$ via elemental microanalysis with the Schöninger method, as summarized in Determination of the Chlorine Content section. Also, with eq. (1), the efficiency of chloromethylation, defined as the percentage of aromatic rings of the polymer that were chloromethylated, was calculated. The results obtained are summarized in Table II.

According to these, it was clear that the chloromethylation conditions had a very strong effect on the actual degree of chloromethylation because the chlorine content ranged from 8.2 to 23.7%. In this table, Y_{CM} indicated that this parameter was around 75% or higher, apart from experiments CM-2 and CM-10. It was remarkable that Y_{CM} of the CM-15 experiment was higher than 100%. This result could be explained either in terms of experimental errors in the determination of %Cl$_{MA}$ or because of the side reactions during chloromethylation that included chlorine atoms within an ether group in the polymer network, as confirmed by FTIR spectroscopy.

Degree of Amination. The degree of amination of the anion-exchange resins was quantified through the measurement of their AEC values by means of the titration of the chloride counterions exchanged by sulfate anions, according to the methodology described in the Measurement of AEC section. In addition, the substitutable chlorine content (percentage by weight) was calculated from the value of AEC (%Cl$_{AEC}$) with eq. (2). Also, Y_{AM} was determined with eq. (3). The results are summarized in Table II. According to these data, all of the resins achieved an AEC value higher than 2.5 mequiv/g. It was also remarkable that the lowest values of AEC were obtained for the solids synthesized with the highest level of the Met factor and the lowest level of the SOCl$_2$ factor (experiments AM-2, AM-6, AM-10, and AM-14). In the case of the other anion exchangers, their AEC values were close to or higher than 4 mequiv/g; this indicated that the AEC reached in most of the experiments was around 85% or higher than the maximum attainable AEC (4.67 mequiv/g), with the assumption that all of the aromatic rings were successfully monoaminated. With regard to Y_{AM}, given by eq. (3), its values were in the range between 95 and 100% for most of the experiments; this indicated that most of the chlorine atoms were replaced by quaternary ammonium groups. Thus, it appeared that most of the chlorine atoms were accessible to ammonium groups and could be replaced by them. This could have been due to the low degree of crosslinking (5.5% DVB) of the precursor P(St–DVB) microparticles.[16] It was remarkable that the value of Y_{AM} of the CM-10 experiment, having the lowest value of degree of functionalization, was much higher than 100%. This disagreement could have been due to a possible higher experimental error associated with the elemental analysis of the samples from the experiments with a lower degree of functionalization.

Response Analysis

Estimation of the Factor Effects. After the determination of the AEC values, the effect of the conditions of the chloromethylation reaction was studied by application of the Yates algorithm.[30] The results of this analysis are summarized in Table III and show that the most important effects were those of the Met and SOCl$_2$ factors. The effect of the Met factor was negative, which meant that when low levels of methylal were used, the AEC value increased, whereas the SOCl$_2$ factor effect was positive.

The effect of the Met factor could be explained by the fact that this substance, besides being the methylating agent, was also the

Table II. Response Values of the Experiments to Manufacture Gel-Type Anion-Exchange Resins

| Experiment Nomenclature | | Response | | | | |
| | | Chloromethylation | | Amination | | |
Chloromethylated	Aminated	%Cl$_{MA}$ (wt %)	Y_{CM} (%)	AEC (mequiv/g)	%Cl$_{AEC}$ (wt %)	Y_{AM} (%)
CM-1	AM-1			3.26	14.3	
CM-2	AM-2	13.2	48.2	3.00	12.9	97.7
CM-3	AM-3			4.43	21.3	
CM-4	AM-4	19.0	76.9	3.99	18.5	97.4
CM-5	AM-5	20.6	85.9	4.40	21.1	102.4
CM-6	AM-6			2.65	11.2	
CM-7	AM-7	22.2	95.4	3.82	17.5	78.8
CM-8	AM-8			4.03	18.8	
CM-9	AM-9			4.17	19.7	
CM-10	AM-10	8.2	27.7	2.81	12.0	146.0
CM-11	AM-11			4.32	20.6	
CM-12	AM-12	18.5	74.2	4.17	19.6	105.9
CM-13	AM-13	21.9	93.6	4.22	20.0	91.3
CM-14	AM-14			3.00	13.0	
CM-15	AM-15	23.7	105.0	4.72	23.2	97.9
CM-16	AM-16			4.30	20.4	

solvent of all of the other reagents used in the chloromethylation, such that a high level (Table I) of methylal implied a lower concentration of the rest of reactants, mainly of the proportion of SOCl$_2$ and polymer. This led to a lower degree of functionalization for the reaction time used. The effect of the SOCl$_2$ factor was consistent with the fact that it was the compound that supplied the chlorine atom during chloromethylation, and therefore, the higher its proportion was, the higher the degree of functionalization was achieved. With a lower influence on the response, the effect of both factors, ZnCl$_2$ and T, were positive. The effect of T could be explained by the fact that a higher T value may have favored the diffusion of the reactants within the microparticles and sped up the kinetics of the reaction because of its influence on the kinetic coefficients. Also, a higher T during the reaction led to a lower concentration of methylal

because a higher temperature promoted a higher evaporation rate for the methylating agent and afforded a larger concentration of other reactants in the reaction medium. With regard to the time factor, its effect was negative, and this could have been due to the side reactions of the chloromethylation process because a longer time led to a higher formation of methylene bridges, a side reaction that removed a chlorine atom already introduced into the polymeric matrix. The methylene bridge reaction would have been more likely to occur at longer times

Table III. Factor and Interaction Effects on AEC

Factor	Effect	Interaction	Effect
Met	−0.67	Met ×·SOCl$_2$	0.47
SOCl$_2$	0.78	Met ×·ZnCl$_2$	−0.12
ZnCl$_2$	0.12	Met ×·T	−0.11
T	0.27	Met ×·Time	0.21
Time	−0.32	SOCl$_2$ ×·ZnCl$_2$	−0.13
		SOCl$_2$ ×·T	0.04
		SOCl$_2$ ×·Time	0.09
		ZnCl$_2$ ×·T	0.07
		ZnCl$_2$ ×·Time	0.03
		T ×·Time	0.22

Table IV. ANOVA Applied to the Analysis of the Effects of the Factors on the AEC Response

Source of variation	Sum of squares	Degree of freedom	Mean of squares	F_0	p
Met	1.82	1	1.82	42.46	<0.01
SOCl$_2$	2.46	1	2.46	57.45	<0.01
T	0.28	1	0.28	6.63	0.05
Time	0.41	1	0.41	9.5	0.03
Met × SOCl$_2$	0.9	1	0.9	20.99	0.01
Met × T	0.05	1	0.05	1.21	0.32
Met × Time	0.17	1	0.17	3.98	0.1
SOCl$_2$ × T	0.01	1	0.01	0.18	0.69
SOCl$_2$ × Time	0.03	1	0.03	0.74	0.43
T × Time	0.19	1	0.19	4.37	0.09
Residual error	0.21	5	0.04	—	—
Total	6.52	15	—	—	—

$F_{0.05;1;5} = 6.61$. F_0- estimated value of the Fisher probability distribution
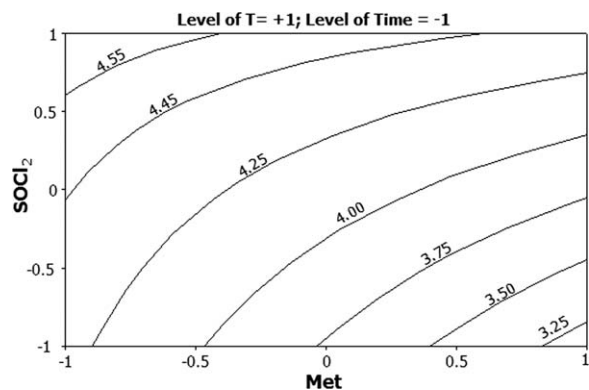
Figure 3. Contour plots for the AEC response generated by eq. (4) with constant levels of T (+1) and time (−1).

because there would have been a higher amount of benzyl chloride residues ready to react with an adjacent aromatic ring and they would have been closer because a higher amount of methylating agent would have been evaporated. With regard to the interaction of the Met and $SOCl_2$ factors, the value shown in Table III indicated an important influence on the response; this means that the ratio between the amounts of methylal and $SOCl_2$ played an important role in the degree of functionalization achieved during the process of manufacturing the anion exchangers based on P(St–DVB) microparticles. Thus, according to the data depicted in Table II, all the experiments had an AEC value above 3 mequiv/g, except those in which the molar ratio between methylal and $SOCl_2$ was higher than 2; that is, experiments AM-2, AM-6, AM-10 and AM-14. This proportion proved to be a high dilution for the chlorinating agent and polymer in the chloromethylation medium, which led to the lowest values of AEC. The other experiments were carried out with a molar ratio between the methylating and chlorinating agent close to a value of 1, as suggested in the literature;[21,32] this led to higher chlorination levels.

Statistical Significance of the Factor Effects. After calculating the effects of the variables, the next step was to determine their statistical significance. However, because the experimental design implemented did not leave any degrees of freedom for calculation of the experimental error, to obtain the statistical analysis of the results, alternative parameters had to be used. One suitable parameter was the pseudo standard error (PSE), according to the Lenth's method.[38] The methodology used to determine it is summarized in Appendix B.

Thus, according to the results of the analysis carried out with Lenth's method, we decided to remove the $ZnCl_2$ factor from further data analysis. Once the $ZnCl_2$ factor was removed, there were already enough degrees of freedom to estimate the variability in the residual error because we assumed that the variability of any factor involving $ZnCl_2$ was random, and hence it was possible to determine the significance of the effect of the factors through an analysis of variance (ANOVA), as summarized in Table IV. The results of the ANOVA gave the values of the F statistics and their corresponding p values for each source of variation studied (the factors and their interactions). From the values calculated for the F statistics, we concluded that

within the range of values investigated, the factors with a significant influence (highlighted in Table IV) on the AEC response were Met, $SOCl_2$, T, time, and the interaction between Met and $SOCl_2$ because the values of their F statistics were higher than the tabulated value ($F_{0.05,1,5} = 6.61$, where 0.05 is the level of significance, 1 is the degree of freedom of the source of variation, and 5 refers to the degrees of freedom of the error).

Correlation Between the Chloromethylation Reaction Conditions and AEC. Furthermore, once the significant effects of the factors and interactions were determined, an empirical model was established by linear multiple regression, as given by eq. (4), in which the value each regression coefficient indicated the relative influence of each source of variation on the AEC response:

$$AEC^e = 3.83 - 0.34x_{Met} + 0.39x_{SOCl_2} + 0.13x_T - 0.16x_{Time} + 0.24x_{Met}x_{SOCl_2}$$
(4)

where AEC^e represents the estimated value of the anion-exchange capacity of the gel-type anion-exchange resins and x_i is the coded level of factor i.

The experimental model given by eq. (4) suggests that to obtain the highest AEC within the range of levels examined in this study, a low proportion of methylal and a high proportion of $SOCl_2$ should be used, in addition to a high temperature of chloromethylation and a short reaction time. Likewise, the model given by eq. (4) includes the interaction between Met and $SOCl_2$, and it has a positive effect on the AEC response. This means that the effects of both factors were not additive, and the difference in the values of the response between the levels of one of these factors was not the same at both levels of the other factor. This was observed in the results for AEC shown in Table IV because the increase in the values of the response was not proportionally the same with increasing concentration of $SOCl_2$ in the reaction medium at both levels of Met. As stated in the Estimation of the Factor Effects section, the molar ratio between the methylating and the chlorinating agent should have been close to a value of 1 to obtain high values of the response. This requirement was fulfilled for three out of four possible combinations of the levels of Met and $SOCl_2$ factors. Thus, experiments AM-2, AM-6, AM-10, and AM-14 carried out with the highest level of Met and the lowest level of $SOCl_2$ and where the molar ratio between Met and $SOCl_2$ factors was higher than 2, afforded AEC values of 3 mequiv/g; these were the lowest AEC results obtained in this study. Accordingly, this result highlighted the importance of the dilution of the reactants because an excessive proportion of methylating agent led to a large dilution of the polymer and $SOCl_2$, in this case with the degree of functionalization decreasing.

Figure 3 shows the contour plot according to the model given by eq. (4). The aforementioned effect of the chloromethylation conditions on AEC of the aminated microparticles was clearly observed. Thus, the best estimated value of the response was obtained with the low (−1) coded level of Met and the high (+1) coded level of $SOCl_2$ factor.

Additionally, because the substitutable chlorine content (%Cl_{AEC}) could be calculated from the AEC values with eq. (2), it was

possible to determine a model that connected the substitutable chlorine content of the gel-type chloromethylated microparticles to the values of the chloromethylation conditions studied through the combination of eqs. (2) and (4). This model is given by eq. (5):

$$\%Cl_{AEC^e} = \frac{13.60 - 1.21 x_{Met} + 1.39 x_{SOCl_2} + 0.46 x_T - 0.57 x_{Time} + 0.85 x_{Met} x_{SOCl_2}}{0.77 + 0.02 x_{Met} - 0.02 x_{SOCl_2} - 0.01 x_T + 0.01 x_{Time} - 0.01 x_{Met} x_{SOCl_2}}$$

$$(5)$$

where $\%Cl_{AEC}{}^e$ represents the estimated value of the chlorine content of the gel-type chloromethylated microparticles (wt %) and x_i is the coded level of factor i.

Both eqs. (4) and (5) can be used in the design of synthesis reactions of functionalized microparticles aimed at attaining predetermined degrees of functionalization and, therefore, obtaining microparticles suitable for some separation and catalysis processes.

CONCLUSIONS

This study was performed to ascertain the quantitative influence of the experimental conditions used in the chloromethylation of polystyrene-based microparticles on the AEC values of the final anion exchanger obtained. The factors studied were Met, SOCl$_2$, and ZnCl$_2$ and the reaction temperature and time. Upon analyzing the results, we found that the proportion of ZnCl$_2$ did not have any significant effect on AEC. Therefore, this factor was removed from the analysis, and a linear regression model that expresses the AEC value as a function of the levels of the significant factors used in the chloromethylation reaction was calculated. This model may be useful for the synthesis of microparticles with specific degrees of functionalization: that is, with the chosen hydrophilicity/hydrophobicity ratio.

According to this model and with consideration of the values of the factors used in this study, the value of AEC increases when a low methylal/polymer ratio, a high level of the SOCl$_2$ factor, a relatively high temperature value, and a shorter reaction time are used. In addition to this, the interaction between methylal and thionyl chloride proved to have a strong influence on the AEC response and was included in the model; this indicated that the effect of these factors was not additive. In fact, the molar ratio between methylal and thionyl chloride had to be held close to unity to increase the degree of functionalization of the microparticles. Because the AEC values were related to those of the replaceable chlorine atoms in the polymeric backbones, a model for the estimation of the available chlorine content was also obtained.

In addition to the foregoing, we found that in most of the experiments, Y_{CM} was above 75%, and the efficiency of the substitution of the chlorine atoms by quaternary ammonium groups was above 85%. According to the results concerning chloromethylation and Y_{AM}, it seemed that some side reactions that included irreplaceable chlorine atoms within the polymer network would have taken place during chloromethylation but also that complete monosubstitution of the aromatic rings to include a chloromethyl group could be achieved because the AEC of some experiments was as high as the theoretical value for the monosubstitution of all of the aromatic rings.

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APPENDIX A: REACTIONS IN THE SYNTHESIS OF ANION EXCHANGER BASED ON P(ST–DVB)

As state in Introduction, the synthesis route for chlomotheylation was that proposed by Galeazzi,[21] whereby methylal was used as a swelling and methylating agent and thionyl chloride was used as a chlorinating agent in the presence of Lewis acids as Friedel–Craft catalysts, as shown in Scheme 1. With the Galeazzi procedure, CMME is also produced in the reaction
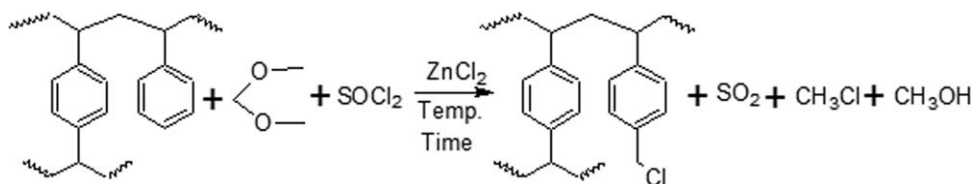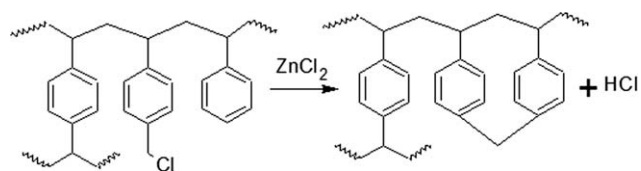

Scheme 2. Methylene bridge reaction.

medium, although its concentration and the temperature at which the reaction occurs are lower.[39] This route was used to achieve linear chloromethylated polystyrene[32] and the chloromethylation of highly crosslinked polystyrene.[40] According to these authors,[32,39,40] the amount of chlorine embedded within the polymeric network would be the theoretical value if all the aromatic rings were monosubstituted, despite the existence of side reactions in the chloromethylation that may either remove chlorine atoms from the polymer by the formation of methylene bridges, as shown in Scheme 2,[10,41] or incorporate potentially irreplaceable chlorine atoms by quaternary ammonium groups (Scheme 3).[37] Therefore, with the existence of side reactions capable of removing some of the previously introduced chlorine and/or of including unreactive chlorine atoms during the chloromethylation process taken into account, it seems that the indiscriminate inclusion of chlorinated groups within the polymeric structure should not be the aim pursued because not all of the chlorine atoms will be available for transformation into the appropriate functional group because of the final application of the microparticles. Instead, it appears to be more useful to search for the introduction of chlorinated groups in which the chlorine may be replaced at a later stage to achieve the intended final functionalization of the polymer, and this was one of the objectives of this study.

The anion-exchange resins were obtained by the replacement of the chloride ion included in the aromatic chlomethyl group by a quaternary ammonium, as shown in Scheme 4.

APPENDIX B: STATISTICAL SIGNIFICANCE OF THE FACTOR EFFECTS: LENTH'S METHOD

As the experimental design implemented did not leave any degrees of freedom for the calculation of the experimental error, we decided to determine PSE according to Lenth's method.[38] This methodology assumes that the variations in the response due to the effects of the variables with a low influence are random. Thus, the first step of Lenth's method is to estimate the effect of the variables with a low influence. To do so, the computation of PSE involves two steps. First, let

Scheme 1. Chloromethylation of P(St–DVB) via the Galeazzi procedure.
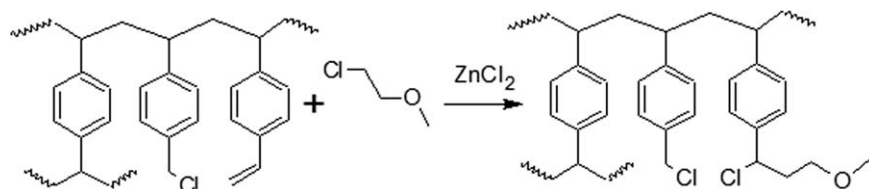
Scheme 3. Reaction of the incorporation of a secondary chlorine atom into the chloromethylated P(St-*co*-DVB) structure.
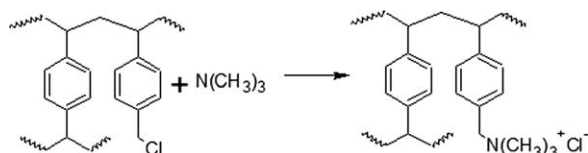
Scheme 4. Amination of chloromethylated P(St–DVB).

$$S_0 = 1.5 \ \text{Median} \ (|\text{Factor effect}|) \qquad (B.1)$$

where s_0 is the Lenth's method parameter. Then, the estimation of PSE is carried out with the following equation:

$$\text{PSE} = 1.5 \ \text{Median} \ (|\text{Factor effect}| : |\text{Factor effect}| < 2.5 s_0) \qquad (B.2)$$

Thus, according to eq. (B.2), the value of PSE is 1.5 times the median of the absolute value of the factor effects that are lower than 2.5 times the value of the parameter s_0. The results of Lenth's method in this case are summarized in Table B.I.
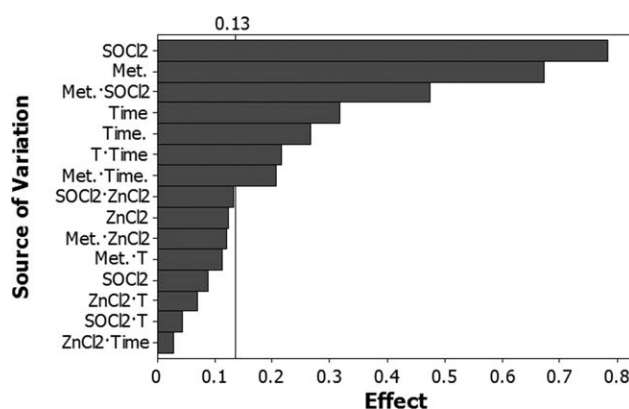
PSE is an estimator of the significance of the factor effects because it is a reasonable estimation of the variance of the effects when there are not many significant effects.[38] Once PSE has been calculated, as summarized in Table B.I, the margin of error (ME) must be estimated to establish a significance level. The ME value was determined with eq. (B.3):

$$\text{ME} = t_{\alpha/2;m/3}\text{PSE} \qquad (B.3)$$

where $t_{\alpha/2;m/3}$ is the t statistic with half of the probability of the significance level chosen ($\alpha = 0.5$ in this case) and a third part of the variation sources ($m = 15$) as the degrees of freedom. Thus, with the tabulated value of $t_{0.25;5}$, which was 0.727, and the value of PSE, which is given in Table B.I, the ME value obtained with eq. (B.3) was 0.13.

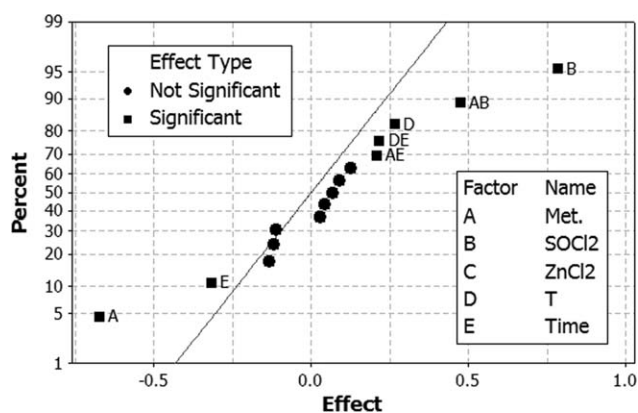**Figure B.1.** Pareto chart of the results of Lenth's method with a level of significance of 0.5.

With regard to the significance level in this step of the study, a value of 0.5 was chosen; we considered that the probability of the inclusion of a factor with a nonsignificant effect among those that were really influential would be increased by the selection of a higher value of the significance level. Consequently, the selection of a significance level of 0.5 for this analysis, which was higher than the usual one, we increased the certainty that when the effect of a factor was classified as nonsignificant, it was really not significant. The result of Lenth's method can be shown as a Pareto chart, as displayed in Figure B.1.

According to Figure B.1, with a level of significance of 0.5, there were significant sources of variation in the AEC response. However, neither the $ZnCl_2$ factor nor any

Table B.I. Estimation of the Values of PSE by Lenth's Method

Term	Calculation	Value
Median (|factor effect|)		|Interaction $SOCl_2 \times ZnCl_2$|
s_0	Equation (B.1)	0.20
Median (|factor effect|:| factor effect| $< 2.5 s_0$)		|Factor $ZnCl_2$|
PSE	Equation (B.2)	0.18

Figure B.2. Normal plot for the factor effects on AEC.

interactions involving the ZnCl$_2$ factor had a significant effect on the response. To check this, the normal probability plot of the effects was elaborated because, in these graphs, the effects that were negligible had a normal distribution and tended to fall along a straight line,[42] as shown in Figure B.2, in which the conclusions drawn from the Lenth's method were confirmed. The interpretation of the normal probability plot of the effects was sometimes very difficult, and this was the reason for the development of the analysis of the results first with an alternative methodology such as Lenth's method and then confirming the conclusions with the normal probability plot of the effects. After the confirmation of the results, the lack of significance of ZnCl$_2$ factor in this study could be interpreted as if, after reaching a certain level of catalyst, any further increase in the concentration of ZnCl$_2$ in the reaction would not provide a higher degree of chloromethylation.[35]