In Situ Quantitative ^{1}H NMR Monitoring of Monomer Consumption: A Simple and Fast Way of Estimating Reactivity Ratios

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ABSTRACT: The copolymerization reactions of acrylic systems of biomedical interest, 2-hydroxyethyl methacrylate (HEMA)/2-acrylamido-2-methylpropanesulfonic acid (AMPS) and *N*,*N*-dimethylacrylamide (DMAA)/AMPS, have been analyzed by ^{1}H NMR. A new methodology is described for the determination of the reactivity ratios based on the quantitative in situ NMR analysis in the course of the copolymerization reaction. The methodology uses the continuous change of the intensity of resonance signals assigned unambiguously to the monomers participating in the polymerization reaction with the reaction time at a given temperature. The evaluation of the monomer concentrations leads to the determination of the instantaneous feed molar fractions and the reactivity ratios, by using a solution of the differential copolymerization equation which describes the terminal model described by Mayo and Lewis. Two approaches to obtain the reactivity ratios by nonlinear fitting of the experimental data to this integrated form are described. The first incorporates the initial conditions as third parameter in the optimization (the values obtained are $r_{HEMA} = 6.81$ and $r_{AMPS} = 0.116$ for the HEMA−AMPS system and $r_{DMAA} = 1.50$ and $r_{AMPS} = 0.40$ for DMAA−AMPS), and the second uses different points as initial conditions in the integrated equation (obtaining $r_{DMAA} = 1.53$ and $r_{AMPS} = 0.36$, in very good agreement with the obtained by the first method). These values are in good agreement with those described in the literature and with data for copolymers prepared at low conversion analyzed by standard methods.

Introduction

It is well-known that the physicochemical properties and biological behavior of polymeric systems depend on the microstructural characteristics of their macromolecular chains which are constructed during the polymerization process by any of the established mechanisms of reaction.[1−6] This is particularly important in the case of free radical copolymerization reactions when monomers of very different chemical structure and reactivity participate.

Among the most characteristic kinetic parameters in copolymerization reactions are the reactivity ratios, which give a clear idea of the average composition and the monomer sequence distribution in statistical copolymer systems.[7,8]

The standard method to determine the reactivity ratios of any monomer pair that fit to the terminal model involves the preparation (at low conversion) and isolation of a series of copolymers with molar compositions all over the range from 0 to 1. After the determination of the feed and copolymer molar fractions, different methods (linear and nonlinear, etc.) can be used to determine the most reliable reactivity ratio values.[9−13] This protocol is tedious, and it has some intrinsic problems and errors: on one hand, the obtained copolymer is not the instantaneously formed copolymer corresponding to the initial feed composition, but it is the average copolymer formed until the copolymerization reaction is terminated at low conversion; although this approximation is well accepted, an unavoidable error encloses this procedure, and it is specially relevant in the cases of very different reactivities, when the instantaneous copolymer has a dissimilar composition compared to the feed. On the other hand, the isolation of the polymer may lead to the presence of residual monomers or solvents and to the possibility of fractioning the copolymer samples.

Recently, several schools have proposed the use of NMR spectroscopy to analyze directly the reaction medium of different copolymerization systems. Ito et al. have described very recently different in situ NMR analysis of radical copolymerization reactions,[14,15] achieving by this method a very complete kinetic study that includes the reactivity ratios determination and simulation of the reaction using these values. Koole and Kruft[16] have studied the free radical copolymerization reactions of new methacrylic esters containing iodobenzoyl groups with methyl methacrylate or 2-hydroxyethyl methacrylate (HEMA) with interest in the biomedical field for the reactivity ratios from several feed compositions polymerized at low and medium conversion degrees. More recently, McBrierty et al.[17] have proposed an elegant and interesting method based on ^{1}H NMR spectroscopy to monitor the real-time curing dynamics of acrylic and vinyl formulations activated by UV radiation. The results obtained from the analysis of the proton spectra of mixtures of HEMA, *N*-vinylpyrrolidone, and 4- or 5-*tert*-butyl-2-hydroxycyclohexyl methacrylate after different times of irradiation gave the molar fraction of these components as a function of the conversion degree. The comparison of the experimental data obtained from the NMR spectra with statistical computer simulation from the *Q*−*e* values was excellent in all the conversion interval, demonstrating the validity of the method for the study of the polymerization of

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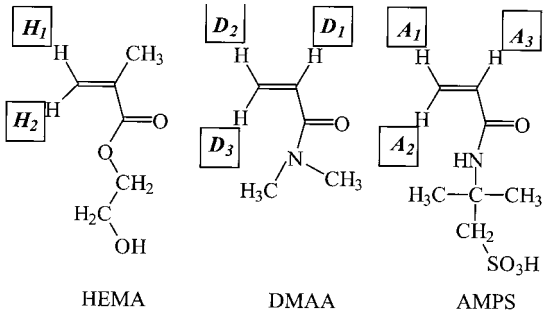

Figure 1. Chemical structures of the monomer used in the copolymerizations together with the nomenclature of the acrylic and methacrylic protons.

complex systems even with the occurrence of cross-linking reactions.

In this work we propose a single methodology for the estimation of the reactivity ratio values. The method uses a solution of the differential copolymer equation which defines the terminal model to fit directly the monomer concentration evolution obtained by the in situ quantitative analysis by ^{1}H NMR spectroscopy. If the reaction obeys the terminal model, a least-squares optimization gives us the best reactivity ratio values. Two different approaches to obtain the reactivity ratios by this treatment are described. This procedure has some advantages compared to the standard one: in addition to the use of in situ monitoring, there is no need to manipulate any sample (for isolation of the copolymers), and it uses instantaneous feed compositions. One controversial point is the possible influence of the magnetic field over the $Q-e$ properties of the monomers and therefore in the copolymerization reaction that has been suggested in the literature.[18] However, the work of McBrierty has shown that this influence is really small.[17] Moreover, the agreement between the reactivity ratios obtained by this method and described in the literature supports the validity of this treatment. This methodology can be expanded to other noninvasive spectroscopic techniques such as FTIR.

These methods have been checked out with the monomer pairs AMPS−DMAA and HEMA−AMPS (the structures of the monomers are represented in Figure 1), which are systems of biomedical interest because of the presence of the sulfonic acid group that is recognized to be one of the responsible components of the antithrombogenic properties of heparine and heparine-like biomaterials bearing active sulfonic groups.[19−21]

Experimental Section

Reagents. 2-Acrylamido-2-methylpropanesulfonic acid, AMPS, was supplied by Sigma and used as received. *N*,*N*-Dimethylacrylamide, DMAA (Aldrich), was carefully distilled under reduced pressure. 2-Hydroxyethyl methacrylate, HEMA (Fluka), was purified according to the literature.[22] Other reagents were extra pure grade and used as purchased.

Copolymerization. The HEMA−AMPS copolymerization reaction was carried out inside the NMR equipment using D_2O as solvent at 50 °C and ammonium persulfate as initiator in a concentration of 0.02 M. The solution was deoxygenated by bubbling nitrogen for 30 min. The total monomer concentration was 0.3 M, and the feed molar fraction of HEMA, 0.50. DMAA−AMPS copolymerization reactions were performed in D_2O at 40 °C, using ammonium persulfate as initiator (0.02 M) and with a total monomer concentrations of 0.3 M. The feed molar fractions of DMAA were 0.75, 0.54, and 0.33. To check the accuracy of the method, low-conversion samples (<5%) were prepared for the system HEMA−AMPS, in the same conditions used for the previous copolymerization reactions but in H_2O and in a thermostated bath. At appropriate times, the reactions were stopped by pouring the solutions into acetone. The precipitated samples were filtered, washed with fresh acetone, and finally dissolved in H_2O and lyophilized before their NMR characterization.

^{1}H NMR Analysis. The experiments were carried out in a Varian 400. To perform quantitative experiments, the following conditions were used: A pulse sequence of 7 μs equivalent to a 90° tip angle and a 60 s delay time were applied in order to allow the total relaxation of the protons and to process the individual data. The spinning rate of the samples was 7 Hz, and for each datum only one acquisition (FID), nt = 1, was used to ensure that the measurement corresponds to instantaneous composition/conversion and not to an average. The sample temperature was maintained at 40 or 50 °C using the heater controller of the NMR equipment. A solution of *N*,*N*-dimethylaminopyridine (DMAP, 10 mg) in D_2O in a thin wall capillary tube introduced in the NMR tube was used as reference. Signals were integrated using the electronic integration of the apparatus after Fourier transform of the FIDs, and the concentrations were determined as follows. In the case of the AMPS−HEMA system:

$$[\text{HEMA}] = \frac{H_1 + H_2}{2R}$$

$$[\text{AMPS}] = \frac{A_1 + A_2 + A_3}{3R}$$

where H_1 and H_2 correspond to the contribution of protons assigned to HEMA in Figure 1, A_1, A_2, and A_3 are the acrylic protons assigned to AMPS in Figure 1, and R are the reference peaks (DMAP). These values were normalized to the initial compositions [HEMA] = [AMPS] = 0.15 mol/L. For the AMPS−DMAA system

$$[\text{AMPS}] = \frac{A_2}{R}$$

$$[\text{DMAA}] = \frac{D_1 + D_2}{2R}$$

where D_1 and D_2 correspond to the contribution of protons assigned to DMAA in Figure 1. The values were normalized using the initial feed compositions.

Discussion

The copolymerizations have been monitored by ^{1}H NMR. Figures 2 and 3 show some spectra of the DMAA−AMPS and HEMA−AMPS systems at different reaction times together with the assignments of the peaks employed in the determination of the monomer concentrations. *N*,*N*-(dimethylamino)pyridine (DMAP) was used as reference for the quantitative analysis of the monomer peaks, and the molar concentrations of the monomers have been determined as detailed in the Experimental Section. From this variation of the monomer concentration, we have determined the reactivity ratios using a well-known integrated form of the copolymerization equation[23,24] (terminal model).

$$\frac{[M_2]}{[M_{20}]} = \left(\frac{[M_{20}][M_1]}{[M_{10}][M_2]}\right)^{r_2/(1-r_2)} \times \left(\frac{(r_1 - 1)([M_1]/[M_2]) - r_2 + 1}{(r_1 - 1)([M_{10}]/[M_{20}]) - r_2 + 1}\right)^{(r_1 r_2 - 1)/[(1-r_1)(1-r_2)]} \quad (1)$$

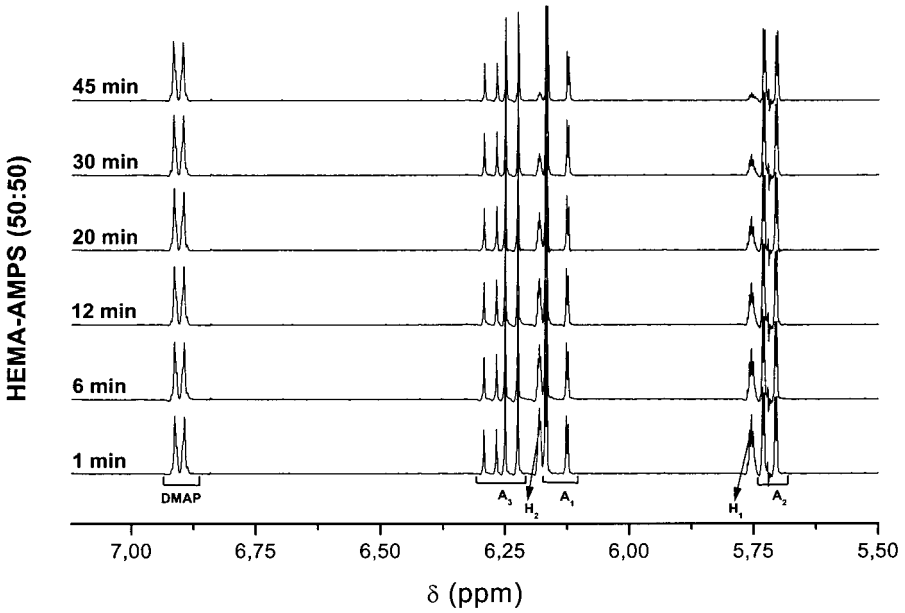

Figure 2. Details of the acrylic region of some representative spectra for the copolymerization reaction HEMA−AMPS with an initial feed molar composition of F(HEMA) = 0.50.

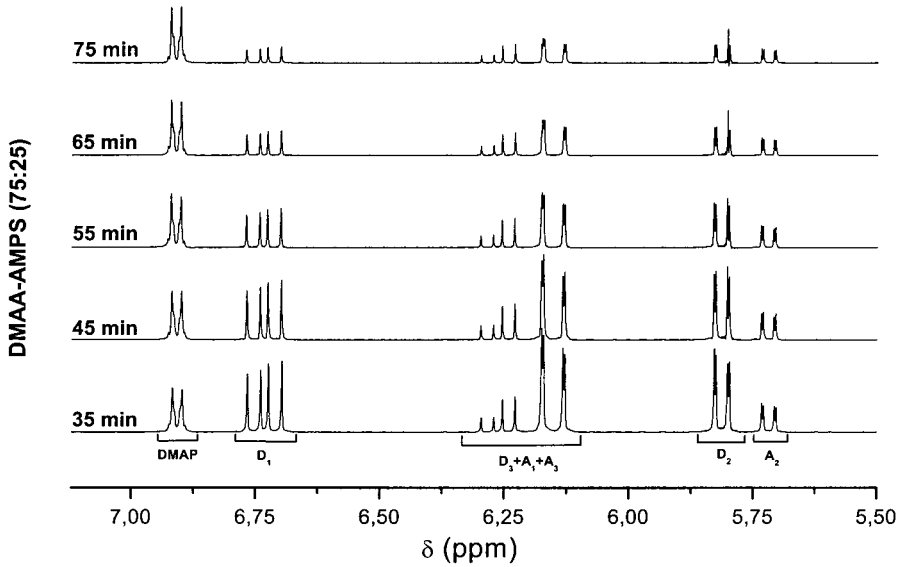

Figure 3. Details of the acrylic region of some representative spectra for the copolymerization reaction DMAA−AMPS with an initial feed molar composition of F(DMAA) = 0.75.

if $[M_1]/[M_2] = x$, $[M_{10}]/[M_{20}] = x_0$, $[M_2] = y$, $[M_{20}] = y_0$, $r_1 = a$, and $r_2 = b$

$$y = y_0\left(\frac{x}{x_0}\right)^{b/(1-b)}\left(\frac{1-b+(a-1)x}{1-b+(a-1)x_0}\right)^{(ab-1)/[(1-a)(1-b)]} \quad (2)$$

$$y = kx^{b/(1-b)}[1-b+(a-1)x]^{(ab-1)/[(1-a)(1-b)]} \quad (3)$$

doing

$$k = y_0\left(\frac{1}{x_0}\right)^{b/(1-b)}\left(\frac{1}{1-b+(a-1)x_0}\right)^{(ab-1)/[(1-a)(a-b)]} \quad (4)$$

where k is the constant that includes the initial conditions. Although this equation is well-known in the literature, the most generally used method for analyzing feed and copolymer composition as a function of conversion is that developed by Skeist[25] which uses cumulative compositions. In our case, to the experimental data x, y ($[M_2]$, $[M_1]/[M_2]$) obtained from the in situ NMR analysis of the copolymer reaction, we have developed two approaches to estimate the reactivity ratios (and the fitting to the terminal model), based on a nonlinear least-squares fitting to eqs 2 and 3.

Figures 4 and 6 show the experimental data obtained from different copolymer reactions for both systems. It can be observed the data dispersion associated to the experimental error of the NMR. There are several factors (sample preparation, integration, etc.) that perturb the measurement, and therefore, the use of a single point as initial conditions (x_0, y_0) can lead to a great error in the estimation of r_1 and r_2 by using eq 2. To overcome this limitation, we have developed two methodologies.

Method 1. We can average the experimental error by using k as the third parameter in the nonlinear

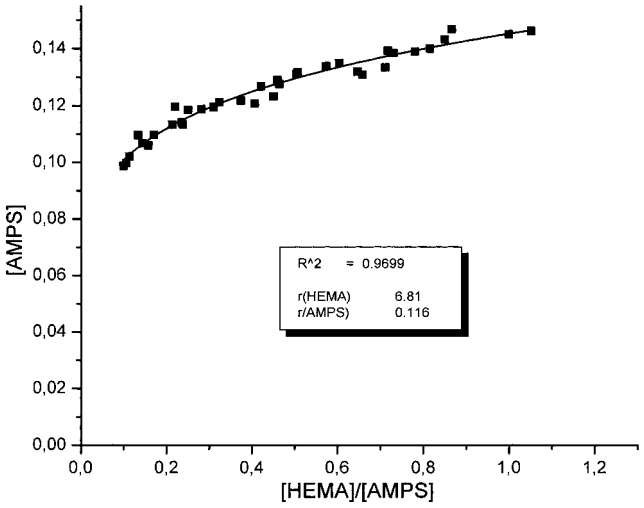

Figure 4. Molar concentration of AMPS, [AMPS], vs the ratio [HEMA]/[AMPS] from the in situ ^{1}H NMR analysis of the copolymeric reaction HEMA−AMPS with an initial feed molar composition of F(HEMA) = 0.50.

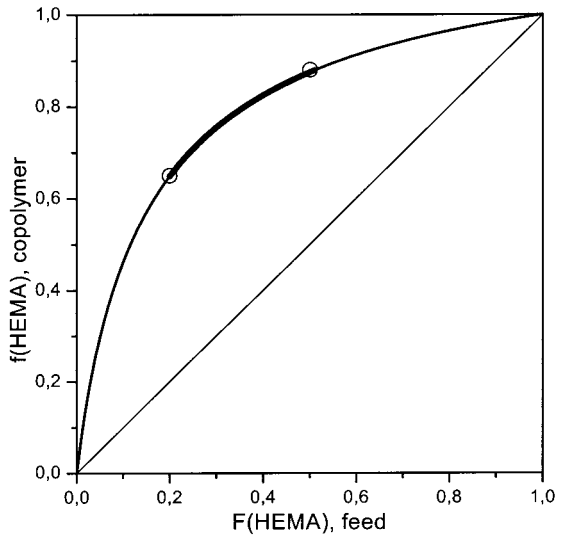

Figure 5. Composition diagram obtained with the reactivity ratios determined by the proposed treatment for the AMPS−HEMA copolymer system. The thick area corresponds to the region covered by the experimental data, and the circles are the data obained from the low-conversion experiments.

fitting (eq 3), instead of using a given x_0, y_0. The least-squares optimization would give us the best r_1, r_2, and k. We have applied this simple treatment to the analysis of the reactions of the comonomers AMPS−HEMA and AMPS−DMAA, which exhibit a very different behavior: while in the DMAA−AMPS system both monomers are consumed at similar rates (which is evidence of reactivities not far from 1), in the HEMA−AMPS system, HEMA is consumed much faster, which means that both monomers have very different reactivities. (The reactivity ratio of HEMA has to be much higher than 1 and the reactivity ratio of AMPS lower than 1.)

As a consequence of that, a good selection of the initial feed concentration in the AMPS/HEMA reaction makes it possible to obtain reliable reactivity ratios from one unique reaction. The variation of the molar concentration of AMPS, [AMPS], vs the ratio [HEMA]/[AMPS] is depicted for a copolymerization with an initial feed molar fraction 0.50 in Figure 4. The higher consumption of HEMA leads to a variation of the [HEMA]/[AMPS] ratio from 1 to 0.1 while [AMPS] decreases smoothly. The fitting to the eq 3 gives the reactivity ratios of r_{HEMA} = 6.81 and r_{AMPS} = 0.116. From these values, the theoretical composition diagram has been calculated (Figure 5), being the thicker segment of the curve the range of feed compositions covered by this single reaction, which seems to be broad enough to estimate these kinetic parameters. The standard reactions prepared at low conversion as reference are also depicted in Figure 5; there is a good agreement to the obtained composition diagram.

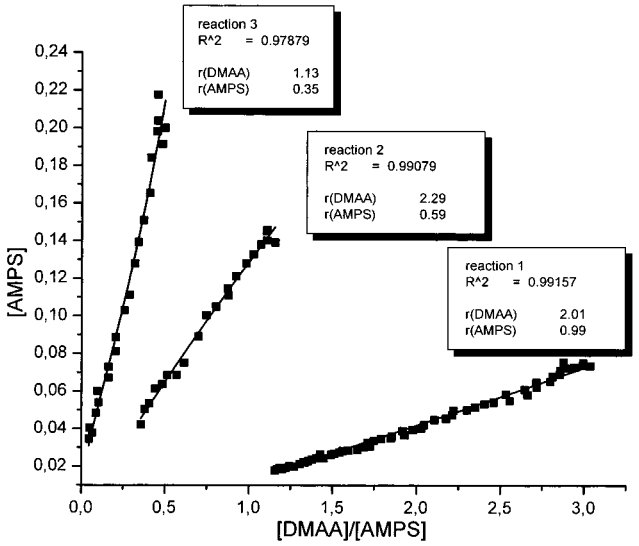

Figure 6. Molar concentration of AMPS, [AMPS], vs the ratio [DMAA]/[AMPS] from the in situ ^{1}H NMR analysis of the two copolymeric reactions DMAA−AMPS with initial feed molar compositions of F(DMAA) = 0.75, 0.54, and 0.33 (experiments 1, 2, and 3, respectively).

In the case of the AMPS/DMAA copolymerization, at high monomer consumption, when we reach the detection limit of the NMR technique, the M_1/M_2 ratio has undergone a small variation, which means at the end a short range of f/F points in the composition diagram. The polymerization reaction continues in any case covering the rest of the composition diagram but under this detection limit. To overcome this limitation, we can start successive experiments with short overlapped M_1/M_2 regions, the initial and the last of the new and previous reactions. The molar concentrations of [AMPS] vs the ratio [DMAA]/[AMPS] is represented in Figure 6 for the three reactions. The independent fitting of the three pairs of data to eq 3 leads to the reactivity ratios of r_{DMAA} = 2.01 and r_{AMPS} = 0.99 and r_{DMAA} = 2.29, r_{AMPS} = 0.59, r_{DMAA} = 1.13, r_{AMPS} = 0.35, respectively. These values give rise to the composition diagrams depicted in Figure 7 where the bulk segments are again the range of feed compositions covered by the reactions. There is a significant disagreement between the three curves, which is related to the well-known error associated with the use of data from short composition regions. To overcome this limitation, we can joint the data of the three reactions by using the shift factors p_1 = $[AMPS]_{fit2}/[AMPS]_{fit1}$ = 8.649 at the common [DMAA]/[AMPS] ratio = 1.156 (the final and the initial M_1/M_2 ratio for the first and second experiment, respectively) and p_2 = 30.763 = $p_1[AMPS]_{fit3}/[AMPS]_{fit2}$ at the M_1/M_2 ratio of 0.45 and $[AMPS]_{fit}$ being the theoretical value obtained from eq 3 in every case. Since x_0 and y_0 have been parametrized and x depends just on the $M_1/$

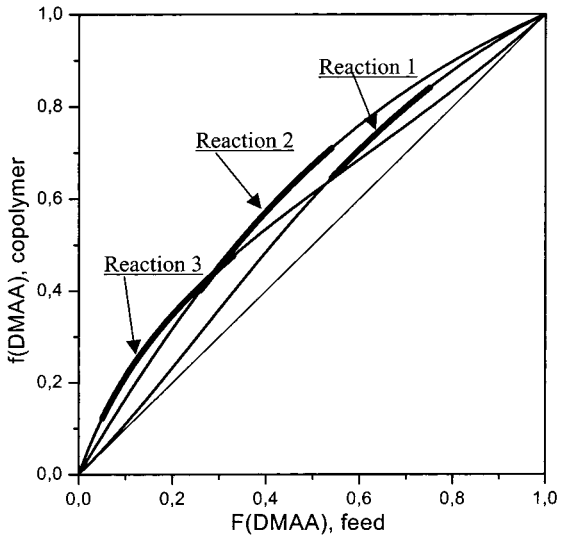

Figure 7. Composition diagrams obtained with the reactivity ratios determined by the first treatment using the independent fit to the data of the three reactions (AMPS−HEMA copolymer system). The thick areas correspond to the regions covered by the experimental data.

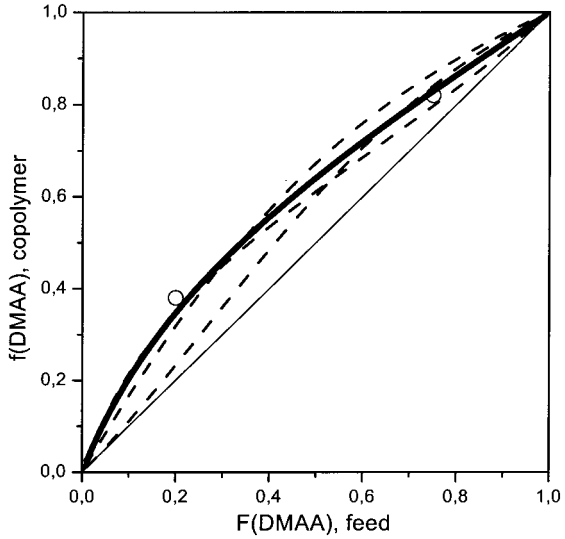

Figure 9. Composition diagram obtained with the reactivity ratios determined by the first treatment using the corrected global data (AMPS−DMAA copolymer system). The dash lines correspond to the diagrams of Figure 7, and the circles are the data obained from the low conversion experiments.

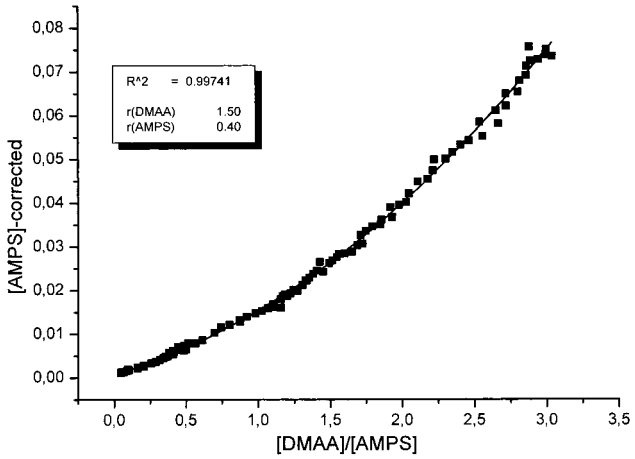

Figure 8. Corrected global molar concentration of AMPS, [AMPS], vs the ratio [DMAA]/[AMPS] using the treatment proposed in the text.

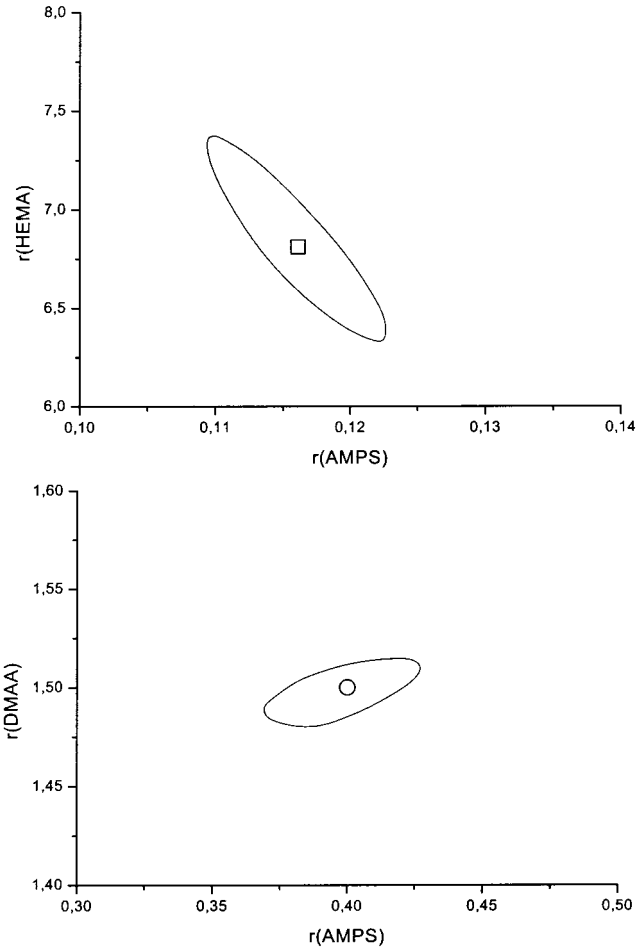

Figure 10. 95% confidence contours for the estimated parameters.

M_2 ratio and not on the absolute concentrations M_1 and M_2, we have create these factors to mathematically compatibilize the data of the three reactions. Multiplying the data of experiments 2 and 3 by $1/p_1$ and $1/p_2$, respectively, we obtain the combined data drawn in Figure 8 which have been fitted to eq 3, leading in this case to the reactivity ratios of $r_{DMAA} = 1.50$ and $r_{AMPS} = 0.40$. In addition to the significant decrease in the error from the nonlinear regression, the theoretical composition diagram obtained from these values (Figure 9) exhibits a coherent agreement with the previous diagrams (Figure 7) because it fits, for the higher DMAA molar fractions, the diagram obtained from the reaction 1 (high initial DMAA feed composition), while for medium and lower molar fractions is in agreement with the diagrams obtained for the reactions 2 and 3 (medium and low initial feed compositions). This result reveals the well-known importance of using data covering most of the composition diagram. In the literature are reported some reactivity ratios for this system,[26] $r_{AMPS} = 0.53$ and $r_{DMAA} = 1.03$, although in this case the authors used samples at high conversion; the error associated to this fact is responsible for these r values closer to the unity than the values found in the present work. There is again a good agreement with the experimental points obtained at low conversion. The 95% confidence contours for the estimated parameters

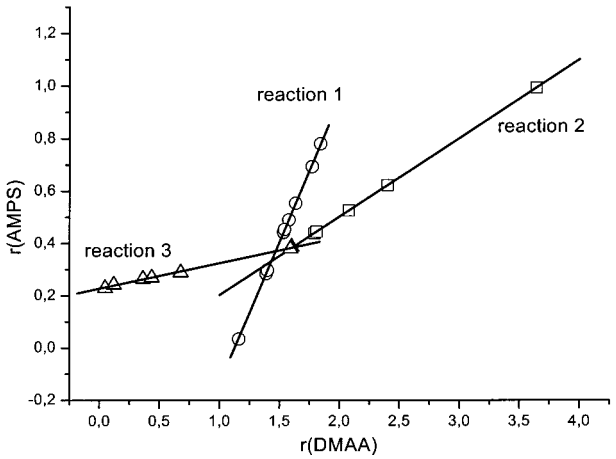

Figure 11. r_{AMPS} vs r_{DMAA} obtained as described in the text (second method).

have been determined using the method described by Box et al.[27] and are represented in Figure 10.

Method 2. An alternative way of obtaining reliable r_1 and r_2 values is summarized in Figure 11. We can apply eq 2 for a given reaction, taken different points as initial x_0, y_0 data. That is, we can consider any given experimental point x_t, y_t as starting point for the rest of the reaction. We have used in this way the first 5−10 points for the three described reactions of the DMAA−AMPS system, and the least-squares optimization to eq 2 leads to the r_1-r_2 data depicted in Figure 11. The data exhibit a particular linear dependence for each experiment. It seems that, for each series of data obtained from one reaction, the experimental error associated with the different x_0, y_0 makes the r_1-r_2 values to displace along a straight line. The reason for this behavior is that the reactivity ratios that fits each sort of experimental data are highly correlated. In fact, the family of composition diagrams that cross a common F/f point (which is a simplification of our case) is described by a linear expression of r_1 and r_2. The crossing point of the lines in Figure 11 has to be the *real* reactivity ratios couple, those independent of the unavoidable error introduced by x_0, y_0 and able to fit the whole copolymer reaction. The more reliable reactivity ratios seem to be 1.53 (r_{DMAA}) and 0.36 (r_{AMPS}), which is in very good agreement with the obtained by the first approach. The advantage of this second compared to the first method is that there is no need of overlapping experimental points, which means a higher versatility since there is no specific requirements for the reactions in order to be used in the treatment.

Conclusions

Two new and easy methodologies to analyze radical copolymerizations by following the decrease of the monomer concentration are described. This protocol used the in situ quantitative analysis by ^{1}H NMR spectroscopy of the disappearance of monomer peaks during the copolymerization to determine the reactivity ratios by using a integrated form of the differential copolymerization equation. The methods have been checked out with the copolymerization systems HEMA−AMPS and DMAA−AMPS. The methods showed that both systems fit the terminal model and led to the simple and reliable determination of their reactivity ratios from only one or two NMR experiments.

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