Anionic Polymerization of *n*-Butyl Cyanoacrylate in Emulsion and Miniemulsion

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ABSTRACT: The manufacture and polymerization of stable *n*-butyl cyanoacrylate (BCA) miniemulsions were achieved in the presence of dodecylbenzenesulfonic acid (DBSA). This surfactant, by releasing protons at the interface, slows down the interfacial anionic polymerization of *n*-BCA through (reversible) termination. Preliminary *emulsion* experiments showed that adequate DBSA/monomer ratios and stirring rates are required to avoid the generation of long polymer chains through uncontrolled polymerization. By sonicating the original mixture to produce a *miniemulsion*, a fair control of oligomer generation is exerted. In all experiments, however, the final oligomer distribution is mainly composed of three to five units, with the equilibrium value imposed by interfacial polymerization/depolymerization events. As a consequence, particles quickly destabilize by Ostwald ripening of the partly water-soluble hydroxylated oligomers. Decreasing the acid content *after sonication* by adding hydroxide sodium permits the formation of longer chains and thus enhances particle stability. Maximum molar masses of 1200 g/mol are reached even in the latter polymerization conditions, a critical chain length for which oligomers lose their surface activity and stop propagating.

Introduction

Cyanoacrylate esters are rated as one of the more reactive monomers[1] in anionic or zwitterionic polymerizations.[2] Traces of weak bases, including water,[3] initiate their polymerizations, and chain termination occurs only in the presence of strong acids or superacids.[4] These properties make cyanoacrylate monomers powerful instant glues for various adhesive applications.[5,6]

Polymerization of alkyl cyanoacrylates is also known to arise in excess water (for a comprehensive review on the subject, see ref 7). Couvreur first developed in 1979 a process to directly generate nanoparticles from methyl or ethyl cyanoacrylates.[8] It consists of adding dropwise the monomer in an HCl solution (pH between 2 and 3) containing a nonionic or polymeric surfactant. Since then, numerous studies described the engineering of nanoparticle preparation which main results are summarized in Table 1.[9] The nature and concentration of surfactant exerts a significant role on the particle size ranging from 25 nm up to few microns (see in particular refs 10 and 11). On the other hand, molar masses are hardly affected by the type of monomer or surfactant chosen.[12−15] Other important factors not visible in Table 1 are the concentrations of reactants (surfactant,[10,12,13,15−19] monomer[11,16,19]) and the pH.[11−17,19,20]

The principle of particle generation was indebted to a micellar emulsion process,[21−23] though no fundamental studies confirmed this statement. In addition, it is only recently that a basic polymerization mechanism scheme was reported in the literature.[24] A complex pathway covering initiation, reversible propagation and reversible termination was proposed to account for the partial control of polymerization in acidic medium (Scheme 1). It confirmed also that, for a given monomer/surfactant system, the pH controls the molar masses and the particle stability.[20,24]

The present emulsion process has been extensively used for preparing nanoparticles of drug vectorization interests, since the poly(alkyl cyanoacrylate) polymer is biodegradable. Still, it entails severe restrictions: (i) low polymer content (generally 1 wt %); (ii) particle aggregation even in a drop-by-drop process; (iii) lack of reproducibility for various batches of monomers (which depends on the content of stabilizer SO_2 in the monomer[14]); (iv) limitation of the number of FDA-approved reactants.

The ionic polymerization in emulsion (IPE) is a research program currently developed in our laboratory. We logically gained interest in studying the cyanoacrylate monomers since they were, until recently, the only monomers known to polymerize anionically in water, apart from cyclosiloxanes. In previous IPE works on heterocyclic (various cyclosiloxanes[25−30] and phenyl glycidyl ether[28,31]) or vinyl (*p*-methoxystyrene[32]) monomers, it was shown that the surfactant both stabilizes the particles and participates to the polymerization: its counterion serves as the initiator of reaction (either hydroxides or protons), and its headgroup forms an ion pair with the propagating species. Studies on cyclosiloxane monomers showed that the interfacial rapid propagation and reversible termination allow one to grow chains even in the presence of water. Molar masses are however limited because chains collapse into the particles while they reach a so-called "critical DP (degree of polymerization)". Besides, at longer times, condensation and redistribution come into play and rise the molar mass of polymer chains together with broadening their distribution. The final result is a stable silicone latex with particle sizes of about 200 nm. Phenylglycidyl ether and *p*-methoxystyrene, respectively anionically and cationically polymerized in miniemulsion, behaved less readily since termination with water is not reversible.

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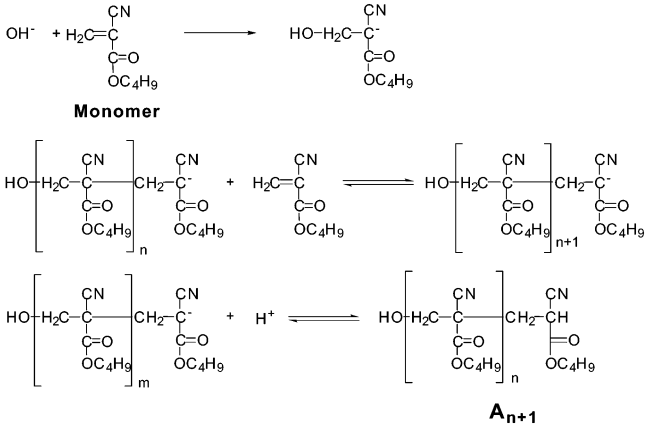
Table 1. Properties of Alkyl Cyanoacrylate Nanoparticle as Reported in the Literature[a]

polymerization process	surfactant	monomer[b]	molar mass (g/mol)	particle size (nm)	refs
(micro)emulsion[c]	PEO/PPO triblock	*n*-BCA,	2800−3500	70−340	10, 18
		i-BCA	550−3400	40−160	12, 16, 21
		i-HCA	3000	35−130	16
		HCA	1500−2400	80−130	12
	chitosan	*n*-BCA		25−85	17
	dextran	*n*-BCA	700−2000	125−810	10, 11, 15, 20, 24
		i-BCA[d]	500−1500	180−500	14
		i-HCA[d]	400−2500	150−380	14
	polysorbate	MCA	800/3000[e]	200	8, 13
		ECA	800−2700	160	13, 42
		BCA	1800−3300	30−160	10, 13
		i-BCA		135	42
		HCA	2200−3000		13
	ethoxylated surfactant	ECA		125	42
		i-BCA		110	42
		n-BCA		30	10
	dextran + PEO/PPO triblock	*n*-BCA		250	18
		i-BCA		300	18
dispersion	*β*-cyclodextrin	*n*-BCA		2700−3450	10
	dextran + PEO/PPO triblock	ECA[f]		950−2200	19

[a] Molar masses reported in the article of Puglisi[42] are not included in this table, since their GPC results seems at odds regarding the other data from the literature. [b] MCA, ECA, BCA, HCA: methyl, ethyl, butyl, hexyl cyanoacrylate, respectively. n, i: normal and iso structures. [c] Particle size (microemulsion, 10−80 nm; emulsion, 100−700 nm) mainly depends on the concentration of surfactant in the recipe. [d] Acid: H_3PO_4 or glycine buffer. [e] Bimodal distribution. [f] Mixture of HCl and H_3PO_4.

Scheme 1



However, all reactions are interfacial and by choosing specific conditions, e.g., type and content of surfactant, cosurfactant, and temperature, the critical DP can also be reached.

On the precepts of previous IPE studies, it seems then possible to slow the polymerization of *n*-butyl cyanoacrylate *by bringing protons at the interface* to induce efficient termination at the monomer/water interface. This is realized by using an acid surfactant, e.g., dodecylbenzenesulfonic acid (DBSA), thus avoiding particle aggregation in a regular emulsion process. Furthermore, stable miniemulsions, i.e., stable monomer droplets of submicronic sizes, can be prepared by ultrasonication, a result not achieved previously.[11] The present article reports the influence of various parameters on anionic *n*-butyl cyanoacrylate (BCA) emulsion and miniemulsion polymerization in the presence of DBSA, focusing more specifically on the mechanism of polymerization and the physicochemistry of such systems.

Experimental Part

***Caution*!** Poly(alkyl cyanoacrylate) handling requires great care as these polymer chains are extremely sensitive to base traces.[1] In the following section, thorough descriptions of experimental and analytical procedures are given to ensure reproducible work.

Materials. Loctite kindly provided BCA, which was stabilized by an unknown amount of methanesulfonic acid. DBSA (97%, mixture of isomers, Janssen) was used as received. Water was doubly distilled and exhibited a low conductometric value (typically less than 2 mS). THF, used in SEC analysis, and CH_2Cl_2, used in polymer extraction (both from Aldrich, analytical grade), were acidified by 5×10^{-4} M of methanesulfonic acid (99.5%, Aldrich) to avoid chain depolymerization.

Typical Polymerization Procedure. A 1 mL sample of *n*-butyl cyanoacrylate was pipetted and added in one shot to a 50 mL DBSA solution (2 g·L^{-1}) in a thick Pyrex beaker. In emulsion, the dispersion was allowed to evolve at various stirring rates using a magnetic stirrer. In miniemulsion, the dispersion was first quickly ultrasonicated during 2 min at 55 W on a Sonifier 450 from Branson Ultrasonic Corp. and then gently mixed at 150 rpm. The natural pH of these dispersions was typically around 2 at the beginning of the polymerization. Assay tubes containing 1 mL of dichloromethane, a spatula of alumina salt, and three drops of methanesulfonic acids were prepared beforehand. Then 1 mL of emulsion withdrawn every minute was added to the tubes. The samples were centrifuged on a bench centrifugator at 3000 rpm during 15 min and left all night to discard the surfactant thin layer between the two phases.

Characterization Methods. pH measurements were carried out on a PHM220 Labmeter from Radiometer (Copenhagen), equipped with a Radiometer XC200 combined glass electrode (reference Ag/AgCl, solution of saturated KCl + AgCl). The apparatus was calibrated using three standard pH solutions (pH 4, 7 and 10) provided by Radiometer.

Particle size measurements were carried out by photon correlation spectroscopy (PCS) only for the miniemulsion experiments. A Zetasizer 4 (Malvern Instruments) equipped with a helium−neon laser (633 nm) and a thermostated cell were used. Samples were diluted with a DBSA solution at concentration (4×10^{-4} M) below its cmc (typically 2×10^{-3} M) to keep the sample pH constant. d_z, *z*-average diameter and Poly, an indicator of the particle distribution ranging between 0 and 1, were measured. Poly values of less than 0.2 indicate monodisperse emulsions, whereas large distributions exhibit values above 0.5.

^{1}H NMR spectra were recorded on a Brüker AC 200 spectrometer in $CDCl_3$ at room temperature, using the following conditions: spectral width 30 ppm with 16 K data points, flip angle of 15°, relaxation delay of 1.4 s, and a digital resolution of 0.36 Hz/pt. The chemical shift scale was calibrated relative of the solvent peak (7.24 ppm). The dichloromethane peak at 5.25 ppm was systematically irradiated.

Table 2. Recipes for All of the Experiments Performed in This Study[a]

run	w_{BCA} (g)	w_{BBSA} (g)	dispersion
1	1.02	0.3	emulsion
2	3.01	0.3	emulsion
3	5.08	0.3	emulsion
4	7.08	0.3	emulsion
5	10.08	0.3	emulsion
6	15.08	0.3	emulsion
7	20.03	0.3	emulsion
8	1.04	0.31	emulsion
9	3.00	0.91	emulsion
10	5.00	1.53	emulsion
11	7.00	2.11	emulsion
12	10.02	3.01	emulsion
13	15.20	4.52	emulsion
14	1.00	0.10	miniemulsion
15[b]	1.00	0.10	miniemulsion

[a] Other parameters: water content, 50 mL; temperature, 25 °C. [b] Addition of hexadecane (5 wt % compared to monomer).

DCI/NH_3 mass spectra were accumulated on a triple quadrupole tandem mass spectrometer R-30-10 NERMAG. An average of 60 scans were accumulated and retreated using the EZSCAN data system of mass evolution. Other operating conditions in the source housing were as follows: electron energy 85 eV, emission current 100 μA, ammonia gas pressure 10^{-4} Torr.

SEC measurements were carried on an apparatus composed of a 515 HPLC pump (Waters), an autosampler S5200 (Viscotek), and a differential refractomer/viscometer S200 (Viscotek). Separation was performed in acidified THF, at a flow rate of 1 mL·min^{-1} and using Shodex columns (KF 802.5L, KF 804L, KF 805L) adapted to the analyses of both long polymer chain and small oligomers.

SEM analyses were performed on a numeric scanning electron microscope STEREOSCAN 440 from LEO company, equipped with a tungsten filament. Samples were first deposited on a glass plate, sputter-coated with gold (10 nm thin), and analyzed on the secondary electron imaging mode.

Results

Preliminary Experiments in Emulsion. This part is intended to deduce the right conditions to fully "control" (or at least slow) the polymerization of *n*-butyl cyanoacrylate. No ultrasonication was carried out here, and agitation rates were set at 150 and 400 rpm for series 1 and 2, respectively. All recipes are compiled in Table 2.

Series 1: Low DBSA Content. The monomer content was increased in the recipe while keeping the surfactant concentration constant (Table 2, runs 1−7). SEC traces from initial, intermediate, and long polymerization times are given in Figure 1.

At initial time, polymers of high molar masses are generated though no macroscopic coagulum forms in the reactor. These polymer chains are presumably formed in the bulk of the big monomer droplets. The average molar masses of the polymer peak rise with monomer concentration (to be compared to elution time for polystyrene standards in Figure 1a), but the polymer content remains almost the same (around 70% according to SEC peak integration). Intermediate and final SEC traces (Figure 1, parts b and c, respectively) show that polymer chains gradually vanish to finally produce a distribution of exclusively small oligomers. Polymerization is thus a *reversible process*. This result is expected from a recent publication where Ryan et al.[1] observed poly(alkyl cyanoacrylate) chain depolymerization in THF containing base traces. The same authors[1] and others[33] proposed also that chains would disappear via

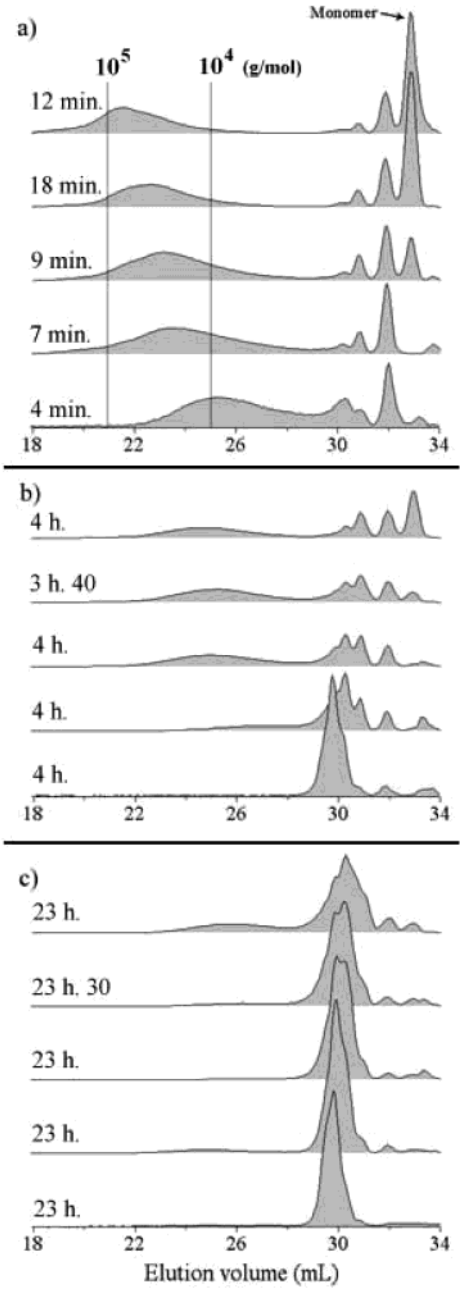


Figure 1. Influence of monomer content on molar masses at initial (a), intermediate (b), and long (c) reaction time in emulsion experiments (series 1, runs 1, 3, 5, 6, and 7 in Table 2; sampling times are reported in the figure). Polymerization conditions: constant surfactant concentration (6 g/L); low stirring rate (150 rpm); monomer content (g, from bottom to top): 1.02; 5.08; 10.08; 15.08; 20.03. Molar masses according to polystyrene calibration are indicated on the top of the figure.

an unzipping process rather than step-by-step depropagation, because no intermediate molar masses were produced during the depolymerization. In the present study, since the average molar mass decreases with time, such a depolymerization/repropagation process would imply that the interfacial concentration of initiator varies with time. To check this issue, pH measurements were performed and are plotted in Figure 2.

The pH of an emulsion takes into account the overall protons present in the dispersion. Since protons at the interface entail an environment that differs from the solution,[34] lower apparent pH value were observed in the emulsion (Figure 2) compared to those in a reference

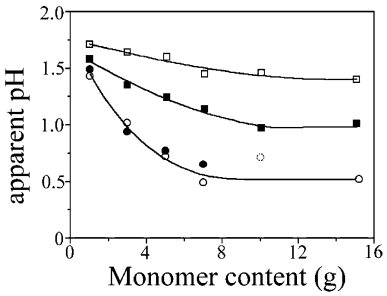


Figure 2. Variations of apparent pH at the beginning (open symbol) and the end (plain symbol) of *n*-butyl cyanoacrylate emulsion polymerization: (□) series 1; (○) series 2 (see text for details).

water solution, for with the pH-meter is calibrated (the pH of a 6 g·L^{-1} DBSA solution is 1.75). This is an indication that DBSA gradually partitions at the interface, the consequence of which is a gradual decrease of polymer chain length by unzipping/repolymerization until all long chains vanished.

Series 2: Constant Monomer/DBSA Ratio. In Table 2 are reported the recipes for experiments carried out at constant monomer/surfactant ratio and decreasing water content (run 8−13). Stable emulsions of increasing brownish color were obtained again without signs of coagulum. SEC traces (Figure 3) show that by increasing the stirring rate, almost no polymer form at initial time (compare runs 1 and 8, Table 2 and Figures 1 and 3, respectively). Oligomer peaks gradually shift toward an equilibrium chain length and pH remains unchanged during the polymerization (Figure 2). A high stirring rate (400 rpm) ensures significant dispersion of the monomer into small droplets. DBSA surfactant readily partitions at the particle surface at initial time and prevents the growing of polymer chains. Polymerization is also slower than for the series 1, especially when decreasing water content (47 h is necessary in best cases to reach the final equilibrium mixture). Since DBSA concentration rises with decreasing water content, the increased interfacial acidity (Figure 2) may be the reason for such low polymerization rates.

Product Characterization. Two samples withdrawn from run 10 (Table 2), at 6 min (sample X) and after 4 h time (sample Y) were chosen for thorough oligomer analyses.

SEC. Figure 4 shows the SEC trace of the two samples X and Y. Sample X is mainly composed of monomer and A_1 oligomer (see structure Scheme 1) whereas sample Y, withdrawn at longer time, is a mixture of oligomers of longer chain length A_n. In both cases, it was checked that little amount of polymer was generated in the conditions of run 10 (less than 10% according to SEC surface area).

Oligomer peaks in the SEC trace are de facto assigned according to their retention time, which decreases with increasing chain length.[35] In a previous study on the ring-opening polymerization of phenyl glycidyl ether in miniemulsion,[31] the open monomer (A_1) peak was coming out at longer elution volume that the monomer one. This delayed elution was due to some interactions with SEC columns from the two-carbinol groups borne by the oligomers. Since the *n*-butyl cyanoacrylate oligomers are monohydroxylated, the A_1 peak elutes before the monomer, as confirmed by ^{1}H NMR (see below).

DCI Mass Spectrometry. Sample Y was subjected to positive DCI mass spectrometry. The spectrogram

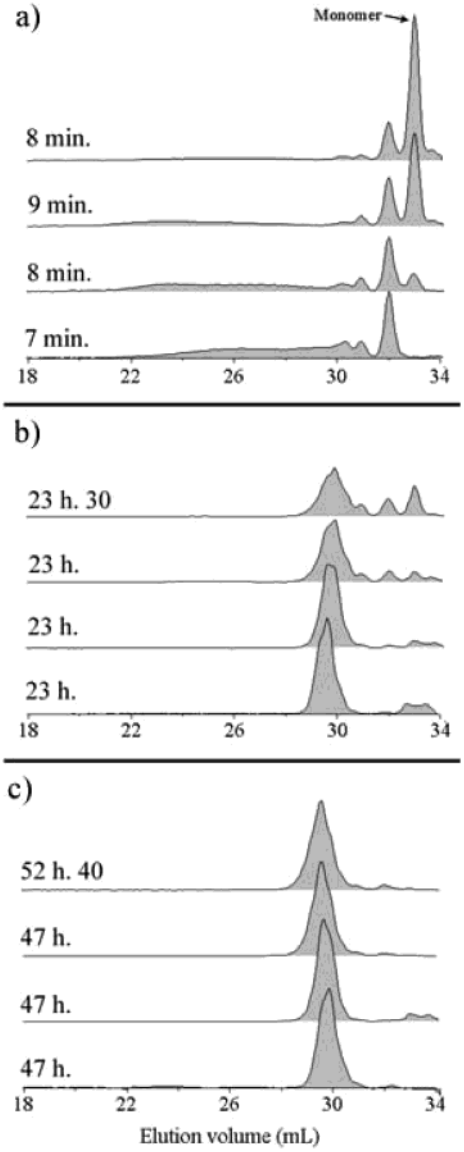


Figure 3. Influence of monomer content on molar masses initial (a), intermediate (b), and long (c) reaction time in emulsion experiments (series 1, runs 8, 9, 11, and 12 in Table 2; sampling times are reported in the figure). Polymerization conditions: constant surfactant/monomer ratio (3.3), high stirring rate (400 rpm); monomer content (g, from bottom to top): 1.04; 3.00; 7.00; 10.02.

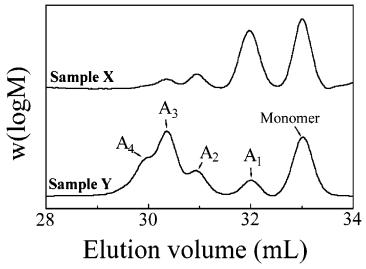


Figure 4. SEC traces of samples chosen for thorough analyses (Table 2, run 10; sampling time: 6 min (sample X); 4 h (sample Y)). For oligomer notation, see Scheme 1.

reported in Figure 5 essentially confirms the presence of monomer as well as oligomers of 1 to 4 units in the sample. Two peaks separated by 30 g/mol show up for all species but the monomer. The main peaks A_i correspond to ammonium ionized oligomers bearing a hydroxide and a proton at both ends, as expected from

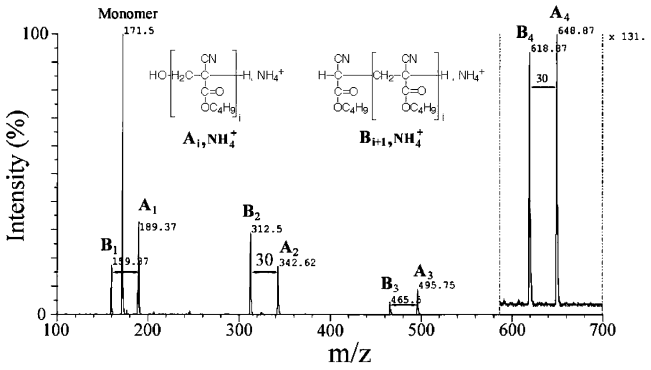
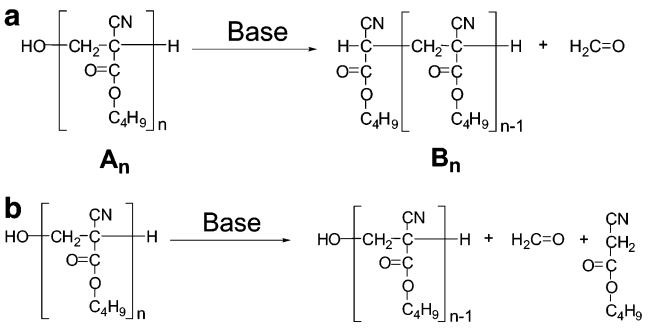


Figure 5. DCI mass spectrometry analysis of sample Y. Structures of corresponding bare and degraded species are also reported on the spectrum (see degradation pathway in Scheme 2a[35]).

Scheme 2



initiation and termination reactions respectively (Scheme 1). The secondary peaks B_i come from the basic attack by the NH_3 gaseous matrix to the α-hydroxymethyl oligomer chain-end (Scheme 2a) that release formaldehyde and *n*-butylcyanoacetate (B_1). Inverse Knoevenagel reaction,[7] i.e., attack of the base on the CH end group, was addressed to explain such degradation (Scheme 2b), a pathway that seems however unlikely (see note[36]).

^{1}H NMR. ^{1}H NMR spectra are given in Figure 6 for sample X (top) and sample Y (bottom). Spectrum for sample X is well resolved and can be fully interpreted, according to chemical shifts reported for the monomer/ethanol adduct[21,37] formed during the nanocapsule preparations. The integration of CH_2 and CH α and ω chain-end peaks is quantitative, confirming the absence of B_i oligomer in the polymerization set (the labile H on the hydroxy extremity exchanges with water and thus cannot be integrated).

^{1}H NMR spectrum of sample Y is rather complex to interpret, due to the presence of numerous oligomers for which chemical shifts vary according to their length. CH_2 peaks from the main chain now appears as a massif centered at 2.5 ppm, whereas chain-end peaks are no longer resolved. Monomer conversion has been calculated by integrated the vinyl peaks compared to the methylene peak at 4 ppm.[38] The obtained value (72%) is close from the conversion given by SEC (70%).[39] In addition, the first oligomer A_1 differs from the others by its missing CH_2 groups between carbons. Integration of CH_2 backbone peak (at 2.5 ppm) compared to the CH_2 peak close from the ester function (4 ppm) or the following CH_2 ester groups gives the content of oligomers of two units or more. The obtained content (around 90%) is quite close to the one observed in GPC (92%) and in any case is much closer than it would be if A_1 and monomer peaks were inverted in the SEC trace

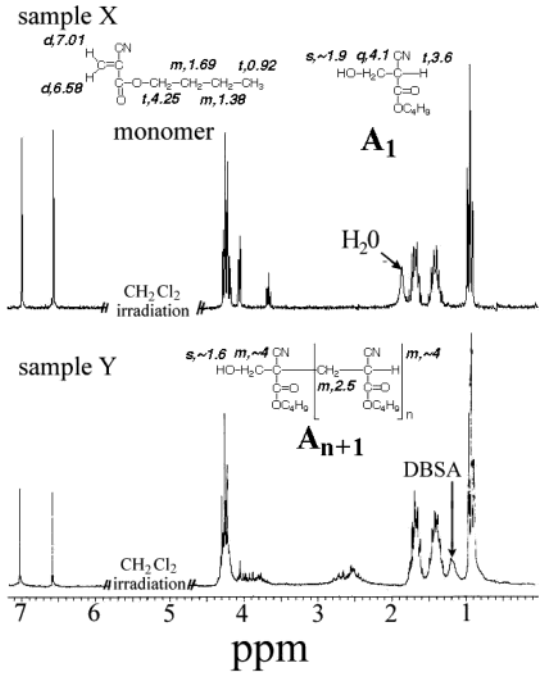


Figure 6. ^{1}H NMR spectra of sample X (containing mainly the monomer and A_1 oligomer) and sample Y (mixture of monomer and longer oligomers). Structures and chemical shifts are also reported in the figure.

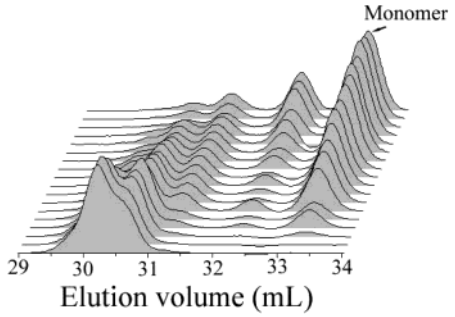


Figure 7. SEC traces as a function of time for a model experiment conducted in miniemulsion (Table 2, run 14). From the top, time of reaction (min): 3, 4, 5, 8, 9, 10, 12, 16, 18, 20, 25, 30, 35, 110, 150, 240, and 5760 (4 days).

(74%). Note finally the peak appearing at 1.2 ppm in sample Y attributed to the alkyl chain of DBSA, which is difficult to remove in polar oligomer-containing samples.

Model Experiment in Miniemulsion. The former emulsion experiments showed that though DBSA avoided uncontrolled particle aggregation, still long polymer chains were generated if the stirring rate and/or the surfactant concentration were too low. The preparation of a miniemulsion, i.e., small monomer droplet dispersion generated by ultrasonication, generates a high specific surface ideally covered by DBSA molecules that avoid polymer generation. In this experiment, a smaller content of DBSA (0.1 g) was added in the recipe (Table 2, run 14) to ensure rapid but traceable polymerization.

Oligomer Contents vs Time. Samples were withdrawn at close times and injected in SEC as shown in Figure 7. Monomer and the A_1 peak monotonically disappear as a function of time. The A_2 oligomer slowly appears and disappears as a function of time, whereas those of longer chain-lengths increase as a function of time. The fact that A_1 and A_2 disappear after being

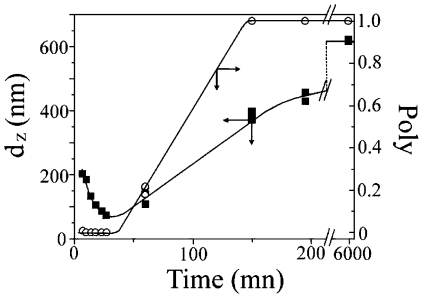


Figure 8. Particle size (■) and polydispersity index (○) evolutions as a function of time in the miniemulsion model experiment (Table 2, run 14). Lines are only guides for the eyes.

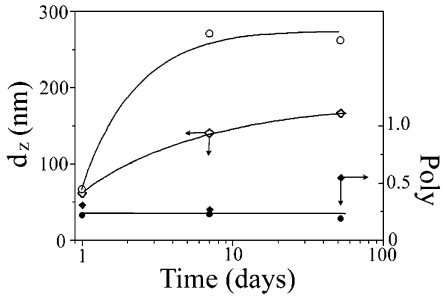


Figure 9. Semilog plot of particle size (open symbol) and polydispersity index (plain symbol) evolutions vs time for a miniemulsion prepared in the presence of 5 wt % hexadecane (Table 2, run 15): (○) bare emulsion; (◇) same recipe, where the emulsion was neutralized quickly after sonication. Lines are only guides for the eyes.

terminated indicates that short chains can be reactivated and thus confirms that termination with DBSA is a reversible process, even for small oligomers. A final equilibrium situation is reached with average oligomer size set around four monomer units.

Particle Size vs Time. Particle size measurements in such sensitive systems is not an easy task, for any variation in pH and/or acid surfactant concentration leads to chain depolymerization/repolymerization, which consequently affects the particle stability. Samples are characterized straight after dilution in a low content DBSA solution, as described in the experimental part. Particle size and size distribution variations with time are given in Figure 8 for the model experiment.

The initial drop in particle size with time is ascribed to the generation of water-soluble oligomers (A_1 and partially A_2) that diffuse out of the particles to reach the water phase. The net result is particle deflating, which affects the particle diameter but not the (narrow) particle size distribution (Figure 8, below 40 min reaction). Oligomers of larger chain length are produced afterward and quickly swell back the particles, which in turn increases their average diameter. The marked increase of the polydispersity index can however not be solely explained by oligomer recovery in the particles. Rather, this result is an indication of Ostwald ripening, i.e., oligomer diffusion through the water phase from small to bigger particles. This process is independent of kinetics considerations and indeed takes place even after the oligomer mixture reaches its equilibrium composition.

Ostwald ripening is usually retarded or slowed by adding a low amount of polymer in the particle, since the latter does not diffuse in the water phase and is swollen by the monomer. This trick cannot be used in cyanoacrylate ester systems, as demonstrated by the first series of experiments where high molar mass polymer disappeared through depolymerization. Even if the particles are very stable in a first stage due to the presence of long polymer chains, similar growth in particle size occurs once the chain length equilibrium is reached. Another way to stabilize the particles is to add a hydrophobe (namely hexadecane) to the monomer prior sonication (Table 2, run 15). The particle size and polydispersity evolutions with time are plotted in Figure 9. Ostwald ripening still arises in the presence of hexadecane, but at much lower rate (to be compared with Figure 8) to give final particles of about 300 nm in size.

Influence of Hydroxide Content. Several attempts to sonicate *n*-butyl cyanoacrylate dispersion at a pH above 2 failed and resulted in coagulum formation. To circumvent this difficulty, a miniemulsion prepared in model experiment conditions (Table 2, run 14) was first led to equilibrium, after which increasing amounts of hydroxide sodium were added.

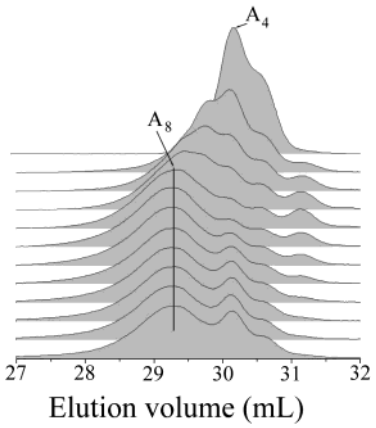


Figure 10. Effect of hydroxide content on oligomer formation in prepolymerized miniemulsion (Table 2, run 15). From the top, [NaOH]/[DBSA] = 0, 0.32, 0.64, 0.97, 1.29, 1.61, 1.93, 2.25, 2.57, 2.90, 3.22, and 3.54.

Oligomer Contents. The resulting SEC traces are given in Figure 10. Increasing the pH shifts the molar mass distribution toward the generation of longer oligomers, but still of limited chain length. Such critical chain-length corresponds to a loss of interfacial affinity resulting in chain entry in the particles, as observed previously in IPE.[25,31,32] As reactions are only interfacial, chains do not propagate anymore. This critical molar mass was also observed in all poly(alkyl cyanoacrylate) dispersion experiments (Table 1), though misinterpreted.[20,24]

For excess NaOH content, more hydroxides are available at the interface and the number of chains increases.[1] Oligomers then depolymerize to reach the average molar mass imposed, in that case, by the ratio initiator/monomer. This result clearly shows that even chains of low molar masses can be depolymerized. It also explains why nanoparticles of alkyl cyanoacrylates vanishes when they are transferred into basic solutions in which depolymerization produces water-soluble oligomers (A_1 and A_2).[40] The hydroxide content is definitively the key parameter in these experiments.

Colloidal Aspects. Oligomers of critical DP size are more hydrophobic than those generated in previous systems and thus diffuse less in water. Ostwald ripening is retarded and particle size gently evolves with time to level off at about 180 nm (Figure 9, bottom curve;

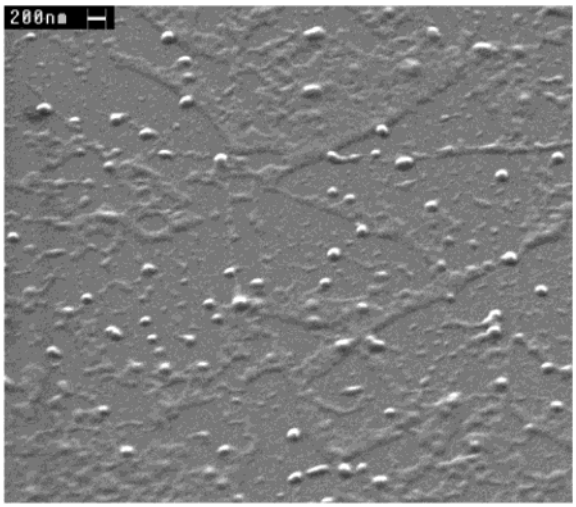


Figure 11. MEB photograph of neutralized poly(butyl cyanoacrylate) miniemulsion (Table 2, run 15; particle size to be compared with final one in Figure 9, series ◇).

same recipe as run 15, Table 2). A MEB image of the final miniemulsion is given in Figure 11. Despite the smoothness of the particles, the MEB size value (average diameter below 200 nm) confirms the PCS results.

Discussion

Polymerization Mechanism. Cyanoacrylate monomers were previously shown to be so reactive that HCl solutions were used as a polymerization media to control the synthesis of nanoparticles. Since reactions in IPE are interfacial, an acidic surfactant was chosen to slow the polymerization rate by inducing termination *at the interface*. The mechanism scheme proposed previously[24] (Scheme 1) on alkyl cyanoacrylate emulsion polymerization in Dextran-stabilized emulsions basically applies to the present polymerization conditions. This study complements the polymerization pathway by putting more light on the location of the various reactants (e.g., surfactant, monomer, oligomers) as proposed in Scheme 3.

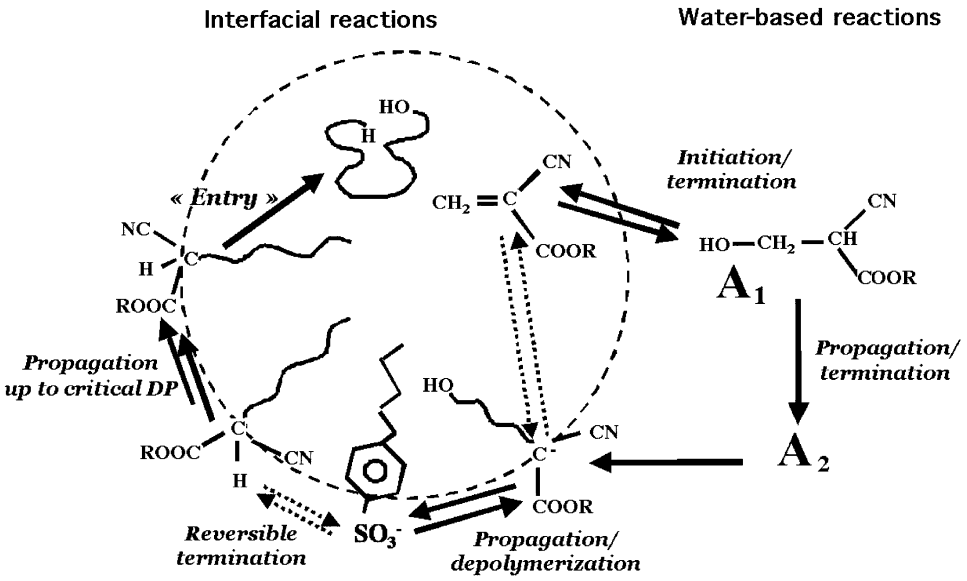
Initiation of chains by OH^- occurs either in water or at the particle interface. Few propagation steps take place in water before the short oligomers entail sufficient surface activity to reach the droplet interface where they further grow. An equilibrium chain length of about four units is finally reached, depending uniquely on the pH of the dispersion. Neutralizing the emulsion results in longer chains formed, albeit limited to a critical chain length of about eight units. At this value, chains entered the particles and stopped propagating. Note that even if large molar mass chains are formed in emulsion conditions, the latter depolymerize in the presence of DBSA to reach similar low molar mass oligomers. At basic pH, excess hydroxide initiator contributes to the fading of the particles by chain depropagation leading to the formation of water-soluble oligomers.

Particle Nucleation Process. Radical polymerization in emulsion is a complex process[41] due to the variety of phases present (water, micelles, monomer droplets, particles). A constant feature however is that polymerization starts and carries on in the water phase until oligomers reach critical sizes, z_{crit} or j_{crit} ($j_{crit} > z_{crit}$) where they enter a particle or precipitate out to form new particles, respectively. Cyanoacrylate ester initiation and first propagation steps follow the same pathway, assuming that initiation takes place in or close to the water phase. In addition, in radical emulsion polymerization, once the nucleation period is finished the number of particles is definitively set and these latter grow by monomer diffusion from the big droplets toward the particles where it polymerizes. Again, according to a previous study,[24] these features are fulfilled in the anionic polymerization of alkyl cyanoacrylates, as demonstrated by a constant number of particles and a large monomer droplet decay. The main difference with radical polymerization, is that, in IPE, propagation takes place at the interface, not in the bulk of the particles, which ultimately produces chains of limited chain length (critical DP ≈ 8).

Conclusion

This study has shown the feasibility of preparing high contents of poly(*n*-butyl cyanoacrylate) nanoparticles in a "controlled" manner. The mechanism of polymerization has also been confirmed, emphasizing particularly the role of the partitioning of surfactant and oligomers on the system. The key point is that poly(alkyl cy-

Scheme 3



anoacrylate) chains are *truly alive*; i.e., any variation in the surrounding environment of the particle favors a depolymerization reaction (this situation is even more dramatic in the presence of DBSA). A similar livingness was very recently proposed in the anionic ring-opening polymerization of propylene sulfide in emulsion.[43] A second-generation process using mixtures of nonionic surfactant, such as pluronic, and *p*-toluene sulfonic acid (next eliminated by dialysis) is currently under study to generate nanoparticles useful for drug vectorization, i.e., where the use of surfactants approved by the FDA is an absolute prerequesite.

The ability of slowing down the system is also academically interesting since it allows one to follow the rates of consumption of monomer and oligomers. A following paper will present both an experimental analysis of SEC traces to derive true concentration variation as well as a kinetic model based on simple polymerization/depolymerization scheme to derive apparent rate constants.[39]

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