Solubilization of phenols by multimolecular aggregates formed by low molecular weight hyperbranched polyglycidol

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Abstract

Hyperbranched polymers have been proposed as potential carriers or host compartments for controlled drug delivery. In this work the solubilization of alkylphenols into aggregates formed by hyperbranched polyglycidol HPG and its ester derivative has been studied. HPG_{17} was synthesized by ring-opening polymerization of glycidol, and then the ester $HPG_4\text{-}RBr_{13}$ has been obtained by reaction of hPG_{17} with 2-bromo isobutyryl bromide. The critical aggregate concentration CAC and micropolarity of aggregates were determined by using pyrene as fluorescence probe. CAC values obtained are 2.5 mM and 0.25 mM, for HPG_{17} and $HPG_4\text{-}RBr_{13}$, respectively. Our results indicate that the hydrophobic effect is larger for $HPG_4\text{-}RBr_{13}$, and that their aggregates are more hydrophobic, than for HPG_{17}. In addition, their sizes and sizes distribution were determined by DLS.

The partition of phenols between the micellar and aqueous phase was studied by using the pseudo-phase model, and the results show that the partition coefficients increases with increasing length of the side alkyl chain, and are larger for $HPG_4\text{-}RBr_{13}$ micelles than for HPG_{17} micelles.

1. Introduction

Hyperbranched polymers (HBP) have received much attention due to their relative ease of synthesis and narrow dispersity [1-4]. The potential use of HBPs in many applications is related to their unique properties, i.e. HBPs are branched polymers with dendritic globular structure and a large number of terminal functional groups. The branching structure of these polymers determine many of their properties, such as viscosity, glass transition temperature, and crystallization behavior [5]. These structures with a hydrophobic core and hydrophilic shell linked by covalent bonds resemble a micellar architecture. As each macromolecule constitutes a single "micelle", there is no critical micelle concentration (CMC), and these systems are referred as unimolecular micelles. Thus, bioactive molecules can be incorporated into their compact and globular structures by simple physical entrapment or by chemical attachment to the terminal functional groups. In this way, a number of active molecules can be conjugated to each unimolecular micelle reaching a high local concentration. These properties have prompted an increasing number of investigations to develop novel HBP for different kinds of applications [6-10].

However, recently it has been shown that amphiphilic HBPs can self-assemble into a diversity of supramolecular structures [11-14]. This is an unexpected and interesting result as it is in contrast to the view of HBP as unimolecular entities. The number of morphologies and structures of assemble HBPs and their unique properties have converted them in promising systems for biomedical applications [15-17]. Self-assembling HBPs are formed by hydrophobic (hydrophilic) dendritic core and hydrophilic (hydrophobic) arms. A multimolecular aggregate mechanism driven by intermolecular interaction between hydrophobic arms has been proposed to explain the formation of large aggregates over 100 nm [18,19].

Hyperbranched polyglycidol HPG is biocompatible polyether with a hydrophilic core and a number of terminal hydroxyl groups. Conjugation of hydrophobic molecules to the terminal groups changes the arms' hydrophobicity and large multimolecular aggregates (MMA) with different shapes can be formed. Formation of large aggregates at a critical aggregate concentration CAC has been reported for HPG in which the terminal hydroxyl groups have been modified by long alkyl chains [20], adamantyl group [21], or amphiphilic chains forming core-multishell structures [19,22,23]. Despite in many applications the encapsulation ability of MMA is a determinant factor; to the best of our knowledge the thermodynamic parameters that control this process have not been studied.

For many applications the incorporation of guest molecules into MMA is a determinant factor; however, to the best of our knowledge the thermodynamic parameters that control this process have not been studied. In this work, the formation of MMA by a low molecular weight HPG and its ester derivative has been studied. The CAC has been determined by fluorescence probing methods, and the distribution constants between the aqueous phase and the pseudo-micellar phase have been measured for a series of alkylphenols. These molecules have been used as model compounds in studies of solubilization of organic molecules into micelles formed by normal surfactants and amphiphilic polymers [24-26]. The thermodynamic parameters obtained are the distribution constants and standard free energy of transfer. Thus, our results can be compared to those obtained with other micellar systems in order to understand the solubilization process and to assess the ability of HPG aggregates to solubilize hydrophobic molecules.

2. Materials and Methods

2.1 Materials

Glycidol (Aldrich), 1,1,1-tris(hydroximethyl)propane TMP (Fluka), 2-bromoisobutyryl bromide (Merck), PMDETA (Aldrich) and p-alkylphenols (Aldrich) were used as received. Polymerizations were carried out following the methodology reported in the literature [1,27,28]. A typical polymerization reaction of glycidol was conducted as follows. Initially TMP was added with mechanical agitation under argon atmosphere into a two-neck round-bottom flask, followed by potassium methylate solution in methanol (20%). The mixture was stirred for several minutes, after which excess methanol was removed by distillation. The temperature was raised to 95 ºC and 25 mL of glycidol slowly added over a period of 12 h using a syringe pump. The product was dissolved in methanol and neutralized by passing through a cation-exchange column. The polymer was precipitated from methanol solution using excess acetone and dried at 80 ºC in vacuum.

Esterification of the hydroxyl groups of HPG was accomplished in pyridine as solvent [28]. The acyl bromide, 2-bromoisobutyryl bromide, was added dropwise at 50 °C. The initial yellow color disappeared and pyridinium bromide precipitated. Pyridine was removed by azeotropic distillation with toluene. The residue was dried with $MgSO_4$ and a pale yellow viscous liquid was obtained.

^{1}H and ^{13}C NMR spectra were recorded in CD_3OD on a Bruker Avance 400 spectrometer operating at 400.1 and 100.6 MHz, respectively (Figures 1-2, Supplementary Material). MALDI-TOF mass spectra were performed with a Microflex mass spectrometer (Bruker Daltonics).

2.2 Dynamic light scattering

The size and size distributions of polymeric micelles were determined by dynamic light scattering (DLS). Aqueous solutions of polymers (1mg/mL) in the absence and presence of p-alkylphenols (10 mM) were prepared with deionized water from an ultrapure water

system (EasyPure II, Barnstead), filtered, and thermostatted at 25°C for 10 m. DLS measurements were performed using a Zetasizer Nano ZS (Malvern Instruments, Malvern, UK) at a scattering angle of 175° to the incident beam provided by a He–Ne laser (633 nm, 4 mW). The resulting data were analyzed using the manufacturer's software (DTS v. 4.2, Malvern Instruments Ltd., Malvern, UK). The hydrodynamic diameter and dispersity index (PDI) are expressed as the average of at least three measurements.

2.3 Fluorescence probing

Samples for fluorescence measurements were prepared by adding a concentrated solution of pyrene in acetonitrile to aqueous solutions of polymers. Steady-state fluorescence spectra of pyrene were recorded utilizing a Horiba Jobin Yvon Fluoromax 4 fluorometer by exciting at 337 nm. All emission spectra were corrected for detector response using a correction curve supplied by the instrument manufacturer. The ratio I_1/I_3 corresponds to the ratio of intensities of peak one ($\lambda = 372$ nm) to peak three ($\lambda = 384$ nm), whereas the ratio I_M/I_E corresponds to the ratio of intensities of the monomer band to the excimer band ($\lambda = 450$ nm).

2.4 Measurement of distribution coefficients

In the pseudo-phase model the solubilization process is represented by the equilibrium

$$S_W \ + \ P_M \ \rightleftharpoons \ S_M \tag{1}$$

For which the equilibrium constant Ks is given by

$$K_S = \frac{[S]_M}{[S]_W [P]_M} \tag{2}$$

where $[S]_W$ and $[S]_M$ denote molar concentration of substrate in aqueous and in the polymeric pseudo-phase, respectively; $[P]_M$ is the concentration of polymer chains forming

the hydrophobic aggregates. On a mole fraction basis the partition coefficient can be expressed by

$$K_X = \frac{X_M}{X_W} \tag{3}$$

where X_M and X_W are the mole fraction of substrate in the micellar and aqueous phases, respectively. In diluted solutions, both quantities are related by

$$K_X = 55.5 \ K_S \tag{4}$$

The distribution coefficients (K_S) were obtained by ultrafiltration using an Amicon 202 cell with a PM5 membrane, which has a MW cut-off of 5,000. Aqueous solutions of PG and PG-Br (10mM and 0.28 mM, respectively) containing different concentrations of p-alkylphenols were filtered, and the absorbances of the filtrate were measured at 275 nm. The molar concentrations of phenols were obtained from a calibration curve. The values of K_S were obtained from the initial slope of a plot of $[S_M]$ against $[S_W]$.

3. Results and Discussion

3.1 Synthesis of hyperbranched polymers

Hyperbranched polyglycidol was obtained by anionic ring opening polymerization of glycidol and using a multibranched initiator. Partially deprotonated TMP was used as the initiator and the anionic polymerization was carried out with slow monomer addition. The polymer was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and MALDI-TOF. The degree of branching (DB) was determined by measuring the intensity of ^{13}C NMR signals, according to the procedure described by Sunder et al. [1] The DB value calculated for HPG is 0.41 that is slightly lower than the value expected for this polymerization. HPG was subsequently esterified with 2-bromoisobutyril bromide to get a more hydrophobic

polymer, HPG-RBr (see Scheme 1). The fraction of –OH groups that were esterified was determined by FT-IR (Figure 3, Supplementary Material). The conversion degree is 78% which is similar to values previously reported [28].

HPG   HPG-RBr
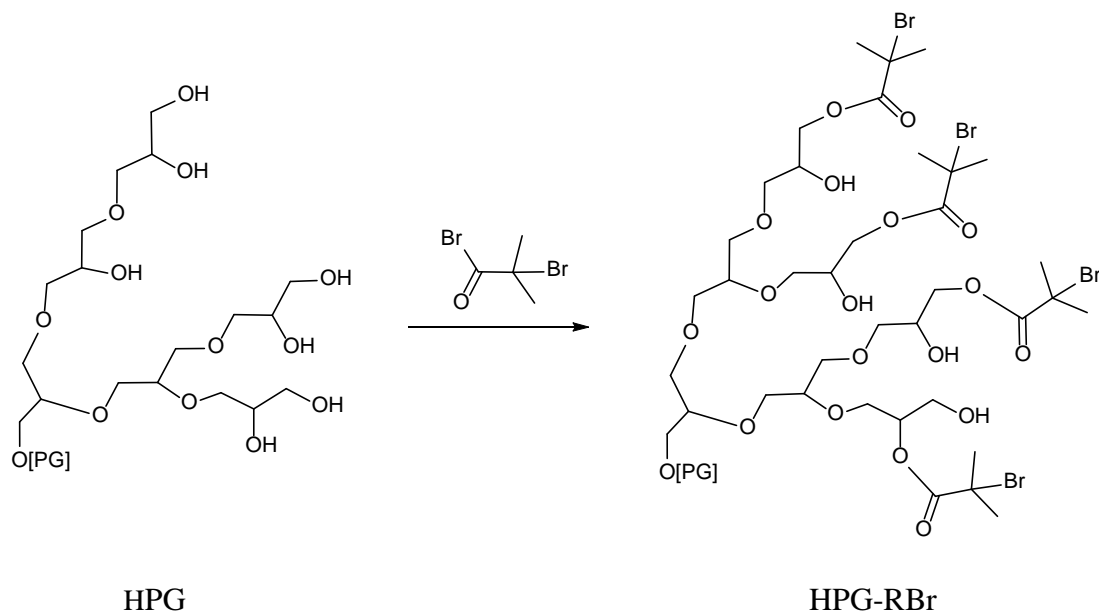
SCHEME 1. Esterification of HPG with 2-bromoisobutyryl bromide

The molecular weights of HPG and HPG-RBr were determined by MALDI-TOF mass spectrometry and the results are given in table 1.

Table 1. Molecular weights of HPG and HPG-Br determined by MALDI-TOF

Polymer	Mn	Mw	Mw/Mn
HPG$_{17}$	1260	1500	1.19
HPG$_4$-RBr$_{13}$	3210	3640	1.13

The results indicate that HPG was obtained with a very narrow dispersity and that esterification with 2-bromoisobutyril bromide brings about an increase of the molecular weight with no change in dispersity. In addition, by comparing the values of Mn for HPG

and HPG-RBr, and considering that for each –OH group that reacts the molecular weight increases by 150 g/mol, it can be concluded that 13 out of 17 –OH groups were esterified. This corresponds to 78% of conversion and it is consistent with the degree of conversion determined by FT-IR.

Therefore, two hyperbranched polymers with different numbers of –OH groups have been synthesized, i.e. HPG_{17} and HPG_4-RBr_{13}.

3.2 Characterization of polymer aggregates

Hyperbranched polyglycidol is a highly flexible polymer that in aqueous solution adopts a globular form with a core-shell structure. Thus, it is expected that HPG_{17} and HPG_4-RBr_{13} form unimolecular micelles at low concentration, and probably multimolecular aggregates at higher polymer concentration. The aggregation of unimolecular micelles to form multimolecular aggregates has been demonstrated for hyperbranched star copolymers [18]. The formation of multimolecular aggregates can be evidenced by detection of the critical aggregate concentration (CAC), i.e. the polymer concentration at which aggregates are formed. The CAC and micro polarity of the aggregates formed by HPG_{17} and HPG_4-RBr_{13} were determined by using pyrene as a fluorescent probe. It is well established that the fluorescence of pyrene changes dramatically with the polarity of the medium, and the ratio I_1/I_3 of the intensities of the bands that appear at 372 nm (I_1) and 390 nm (I_3) has been used to monitor conformational transitions in polyelectrolytes containing carboxylic groups in the side chain, and self-aggregation of amphiphilic copolymers [29-32]. To determine the CAC the ratio I_1/I_3 was measured as a function of both HPG_{17} and HPG_4-RBr_{13} concentrations. A plot of this ratio against polymer concentration is shown in Fig. 1.
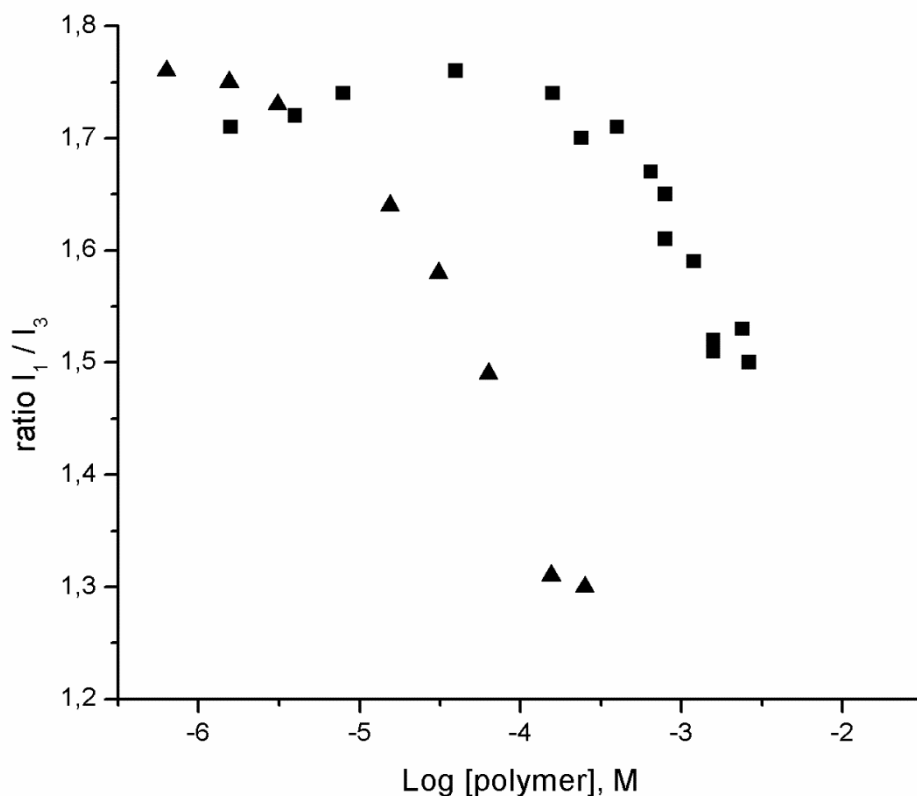
Figure 1. Plot of ratio I_1/I_3 against the logarithm of the polymer concentration: HPG_{17} (■); HPG_4-RBr_{13} (▲)

At low concentrations of both polymers the values of I_1/I_3 are lower than the value measured in aqueous solution. These results confirm that HPG polymers form unimolecular micelles providing a microenvironment for pyrene even at the lowest concentration used. The polarity of this environment is quite similar to water due mainly to the flexibility of the dendritic polymer which allows easy entry to water molecules. This flexibility might be due to the low degree of branching and the presence of ether bonds in the dendritic structure. With increasing polymer concentration the value of I_1/I_3 decreases steeply, until a constant value is reached. This breaking point is associated with the critical aggregate concentration,

whereas the limiting values of I_1/I_3 represent the polarity sensed by pyrene in the hydrophobic sites provided by polymer aggregates. CAC values obtained from Fig. 1 are 2.5 mM and 0.25 mM for HPG_{17} and HPG_4-RBr_{13}, respectively. These CAC are much higher than those measured for branched poly(ethylene imine) functionalized with long alkyl chains and monomethyl poly(ethylene glycol) mPEG [33]. For the latter, the CAC values are in the range 10^{-7} to 10^{-5} M, which suggest a high stability of the multimolecular aggregates. This effect was attributed to the interaction between long aliphatic chains [33]. The same explanation has been given for the aggregation of HPG derivatized with C_{18} alkyl chains and mPEG [34], even though in this case no CAC could be determined by solubilization methods because the aggregate collapse with the addition of solute molecules. Thus, the main driven force for aggregation of these HPG might be the hydrophobic interaction of ether chains or 2-bromoisobutyrate groups. In addition, the formation of hydrogen bonds could make an important contribution for aggregation of unimolecular micelles of HPG_{17}. On the other hand, the limiting values of I_1/I_3 are 1.50 and 1.30 for HPG_{17} and HPG_4-RBr_{13}, respectively. These results indicate that HPG_4-RBr_{13} multimolecular aggregates are more stable and more hydrophobic than those formed by HPG_{17}. These effects arise from a reduced number of –OH groups, forming the outer corona, and the presence of 2-bromoisobutyrate groups in the hydrophobic dendritic core.

It has been shown that in polymer micelles having a core-shell structure, non-polar molecules are distributed between the core and the inner corona [35,36]. The distribution of pyrene has been demonstrated by quenching of pyrene fluorescence by nitromethane, a water-soluble molecule [36]. Results indicate that pyrene located in the corona is more exposed to water, and therefore is more efficiently quenched by nitromethane relative to that localized in the core. As consequence of this preferential quenching the plots of I_0/I

against quencher concentration are not linear, as would be predicted by the Stern Volmer equation, and show a downward curvature. In Fig. 2 are presented Stern-Volmer plots for the quenching of pyrene (1.0 μM) in aqueous solutions of hyperbranched polymers at concentrations above the CAC, i.e. 1.0 x 10^{-2} and 2.8 x 10^{-4} M for HPG_{17} and $HPG_4\text{-}RBr_{13}$, respectively. These results indicate that pyrene is clearly distributed between two different environments, one of them being more difficult access by water soluble quenchers.
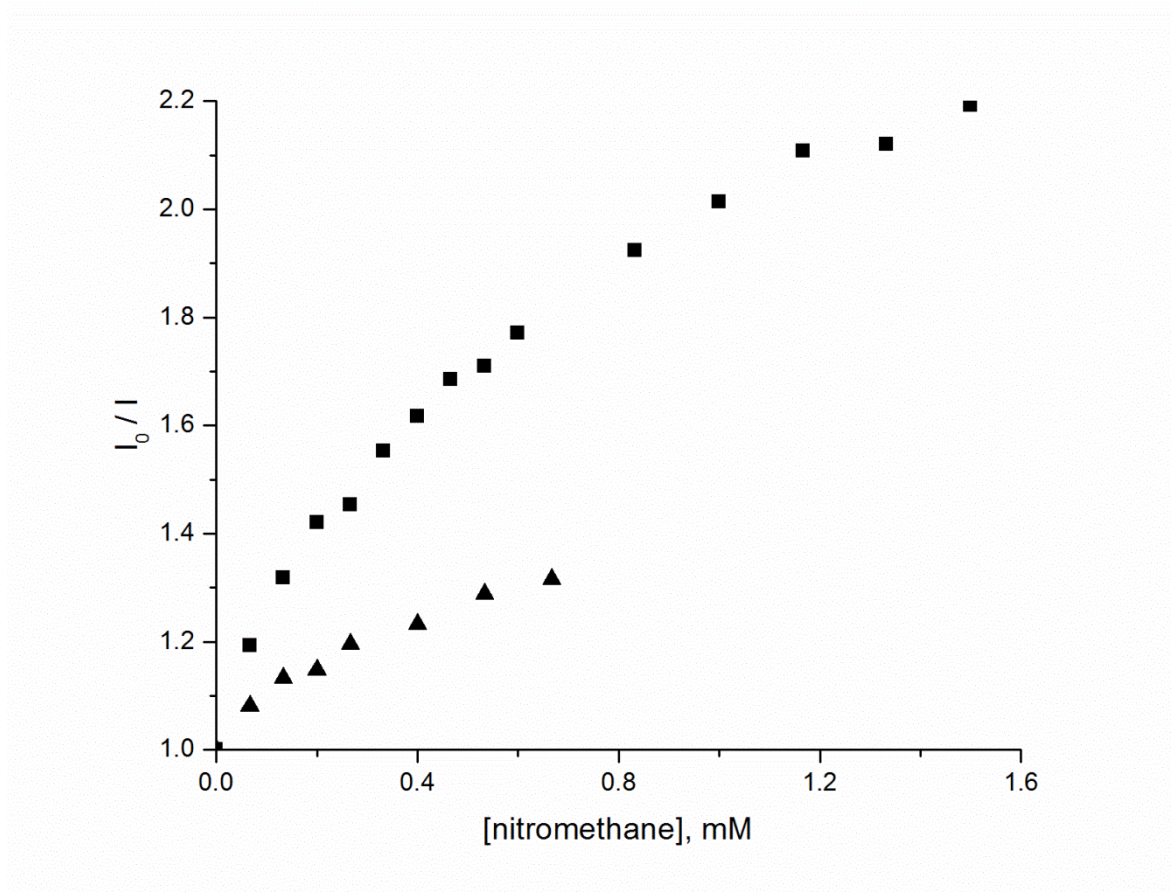

Figure 2. Quenching of pyrene fluorescence by nitromethane in aqueous solution of HPG_{17} (■) and $HPG_4\text{-}RBr_{13}$ (▲). [Pyrene] = 1 μM; $[PG_{17}]$ = 10 mM; $[PG_4\text{-}RBr_{13}]$ = 0.28 mM.

The fraction of pyrene that is more exposed to water can be determined using equation 5:

$$\frac{I_0}{I_0 - I} = \frac{1}{fK_{SV}[Q]} + \frac{1}{f} \tag{5}$$

where K_{SV} is the Stern-Volmer constant, f is the fraction pyrene more accessible to water, and [Q] is the nitromethane concentration [37]. Plots of the results according to Eqn. 5 are linear for both polymers and the fraction f was obtained from the intercept (Fig. 3).
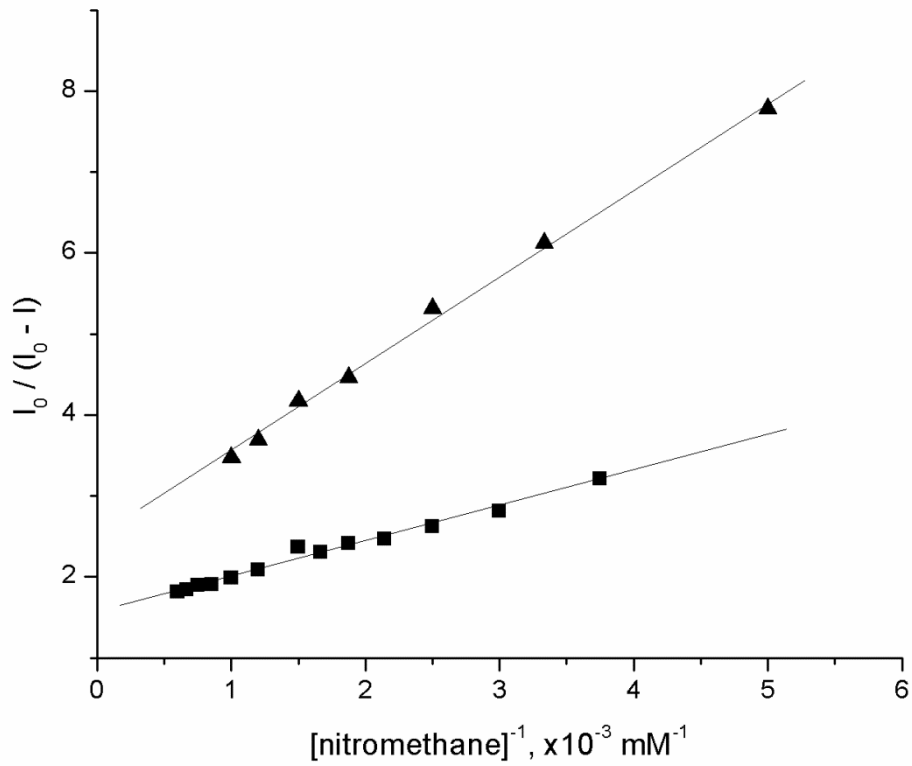

Figure 3. Modified Stern Volmer plot for quenching of pyrene fluorescence by nitromethane in HPG_{17} (■), and $HPG_4\text{-}RBr_{13}$ (▲) micelles

The values of f are 0.64 and 0.40 for HPG_{17} and $HPG_4\text{-}RBr_{13}$ aggregates, respectively. This means that most of the pyrene solubilized by aggregates formed by HPG_{17} is easily quenched by nitromethane, whereas in $HPG_4\text{-}RBr_{13}$ aggregates around 60% of the pyrene

molecules are inaccessible to nitromethane. These results are consistent with the measured values of the ratio I_1/I_3, which suggest that the HPG_{17} aggregates are more accessible to water molecules. The lower accessibility of nitromethane to the HPG_4-RBr_{13} aggregates may be attributed to a reduced flexibility of HPG chains due to the higher hydrophobic effect acting on the esterified chains.

The sizes and sizes distribution of aggregates were determined by DLS. The results shown in Fig. 4 indicate that at concentration below the CAC HPG_{17} form structures with hydrodynamic diameters of 3.5 and 22 nm, whereas above the CAC the diameters change to 30 and 130 nm. For HPG_4-RBr_{13} two multimolecular aggregates with hydrodynamic diameters of 40 and 180 nm can be observed. Interestingly, in Fig. 5 it can be seen that the addition of p-alkylphenols to HPG_{17} aggregates induces changes in the size distribution, i.e. the distribution is shifted to slightly larger sizes and the smaller aggregates disappear. This result is completely opposite to the behavior reported for HPG-C_{18}-PEG copolymers where solubilization of pyrene molecules induces a transition from multimolecular aggregates to unimolecular micelles [34]. On the other hand, for polymer micelles formed by linear block copolymers it has been found that solubilization of phenols and other additives induce micellar growth [38-40].
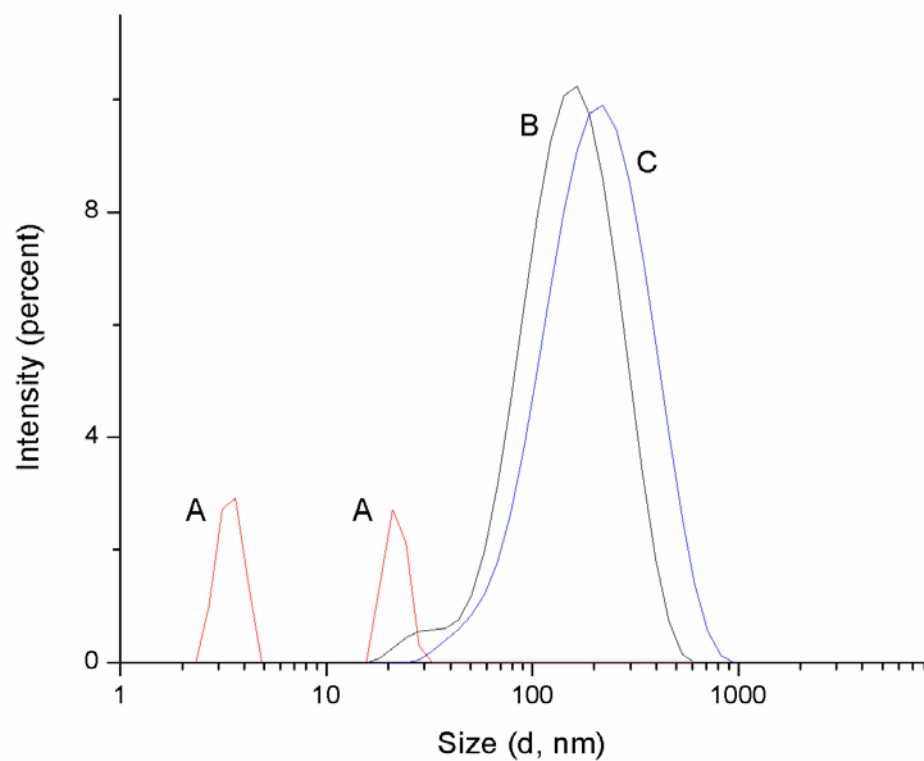
Figure 4. Hydrodynamic volumes of aggregates formed by: (A) HPG_{17} (0.7 mM); (B) HPG_{17} (10 mM); (C) HPG_4-RBr_{13} (0.28 mM). DLS measurements were made at 25 °C.
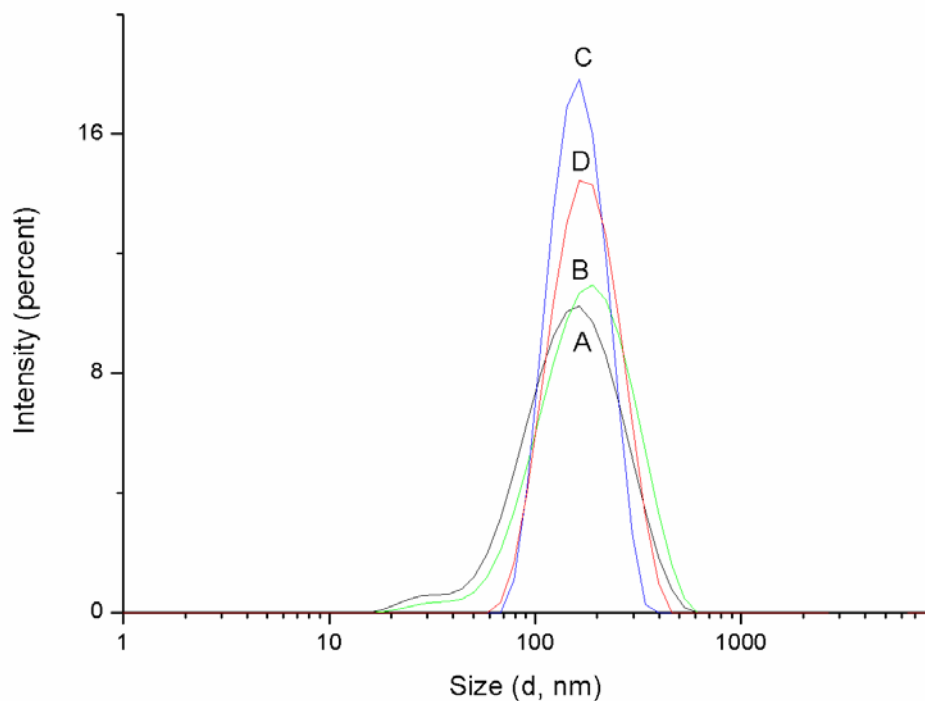
Figure 5. Hydrodynamic volumes of aggregates formed by HPG_{17} (10 mM) in absence (A) and presence of p-cresol (B), p-ethylphenol (C), p-butylphenol (D). DLS measurements were made at 25 °C. [Phenols] = 10 mM.

3.3 Distribution of p-alkylphenols between aqueous phase and polymer aggregates

The partition of phenols between the polymer and aqueous phase were determined for HPG_{17} and HPG_4-RBr_{13} by using the pseudo-phase model. The distribution coefficients were obtained from the initial slope of the plots shown in Fig. 6 according to Eq. 2.
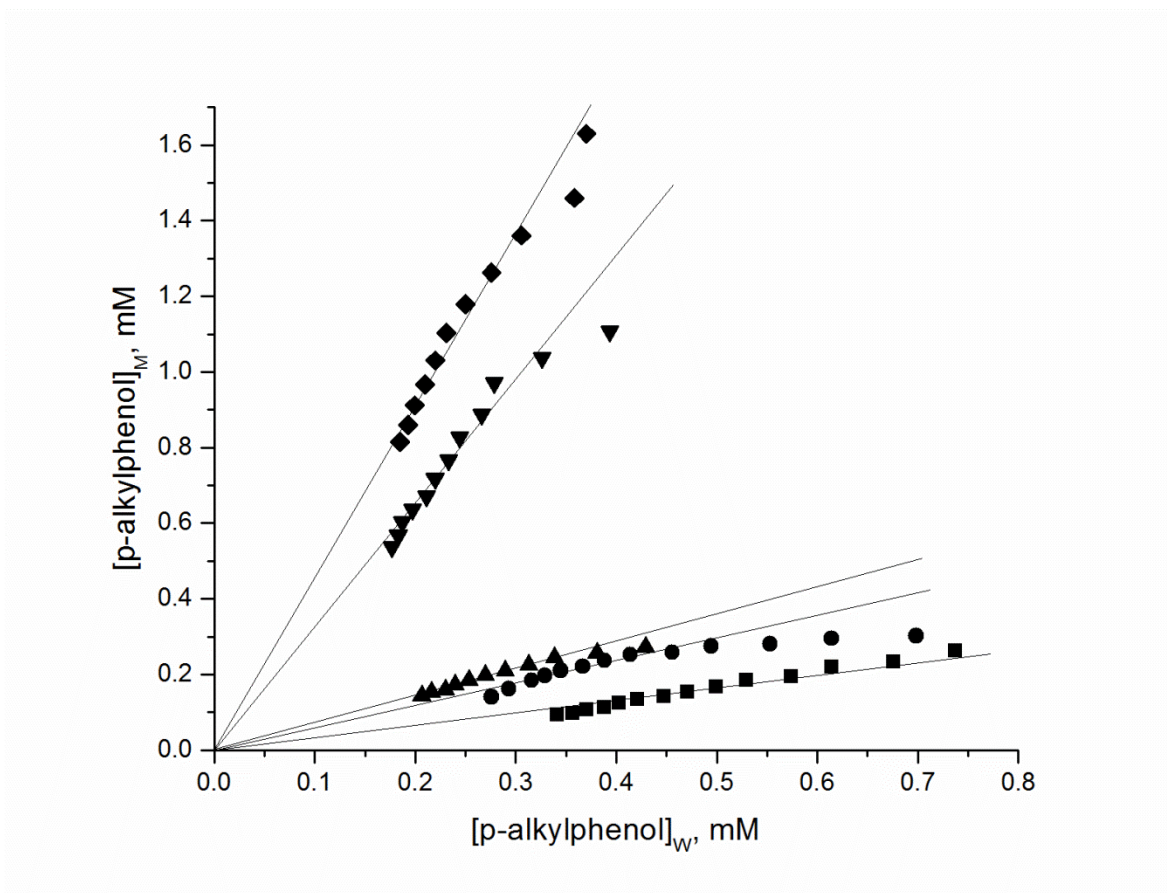
Figure 6. Measurements of distribution coefficients of p-alkylphenols between aqueous and polymer pseudo-phases, K_S values are obtained from the initial slope. (■) p-ethyl phenol, (●) p-propyl phenol, (▼) p-butylphenol, at $[PG_{17}]$ = 10 mM; (▲) p-propylphenol, (♦) p-butylphenol at $[HPG_4-RBr_{13}]$ = 0.28 mM

The partition coefficient in a mole fraction basis K_X is related to K_S through Eq. 4, and all calculated values are summarized in Table 2. The results show that the partition coefficients increases with increasing length of the side alkyl chain, and are larger for HPG_4-RBr_{13} aggregates than for HPG_{17} aggregates. This behavior is in line with what has been reported for distribution of phenols in normal micelles, unimolecular and interpolymer micelles [24-26,41].

Table 2. Partition coefficients and standard free energies of transfer of p-alkylphenols between aqueous phase and polymer phases

	HPG$_{17}$			HPG$_4$-RBr$_{13}$		
p-Alkylphenol	K_S	K_X, x 10^4	$\Delta\mu_t^0$, kJ mol^{-1}	K_S	K_X, x 10^4	$\Delta\mu_t^0$, kJ mol^{-1}
p-cresol	60	0.3	−19.97			
p-ethylphenol	420	2.3	−24.90	1160	6.4	−27.40
p-propylphenol	900	5.0	−26.80	2610	14.5	−27.45
p-butylphenol	4865	27.0	−31.00	16750	93.0	−34.00

The relationship between the partition coefficient K_X and the standard free energy of transfer from the aqueous phase to the pseudo-micellar phase is given by

$$\Delta\mu_t^0 = \mu_M^0 - \mu_W^0 = -RT\ln K_X \tag{6}$$

It has been shown that $\Delta\mu_t^0$ can be separated in additive contributions from different constituent groups of the transferred substrate [24,42]

$$\Delta\mu_t^0 = \Delta\mu_{Ar}^0 + n_C\Delta\mu_C^0 \tag{7}$$

where $\Delta\mu_{Ar}^0$ denotes the contribution of the parent aromatic group, $\Delta\mu_C^0$ is the incremental free energy per methylene group, and n_C is the number of these groups attached to the parent group. Similar linear free energy relationships have been found in studies of partition of solutes between aqueous phase and organic solvents, micelles, and polymer micelles [24,25,42-44]. Plots of the values of $\Delta\mu_t^0$ against the number of carbon atoms in the alkyl group are almost linear for both polymer aggregates (Fig. 7).
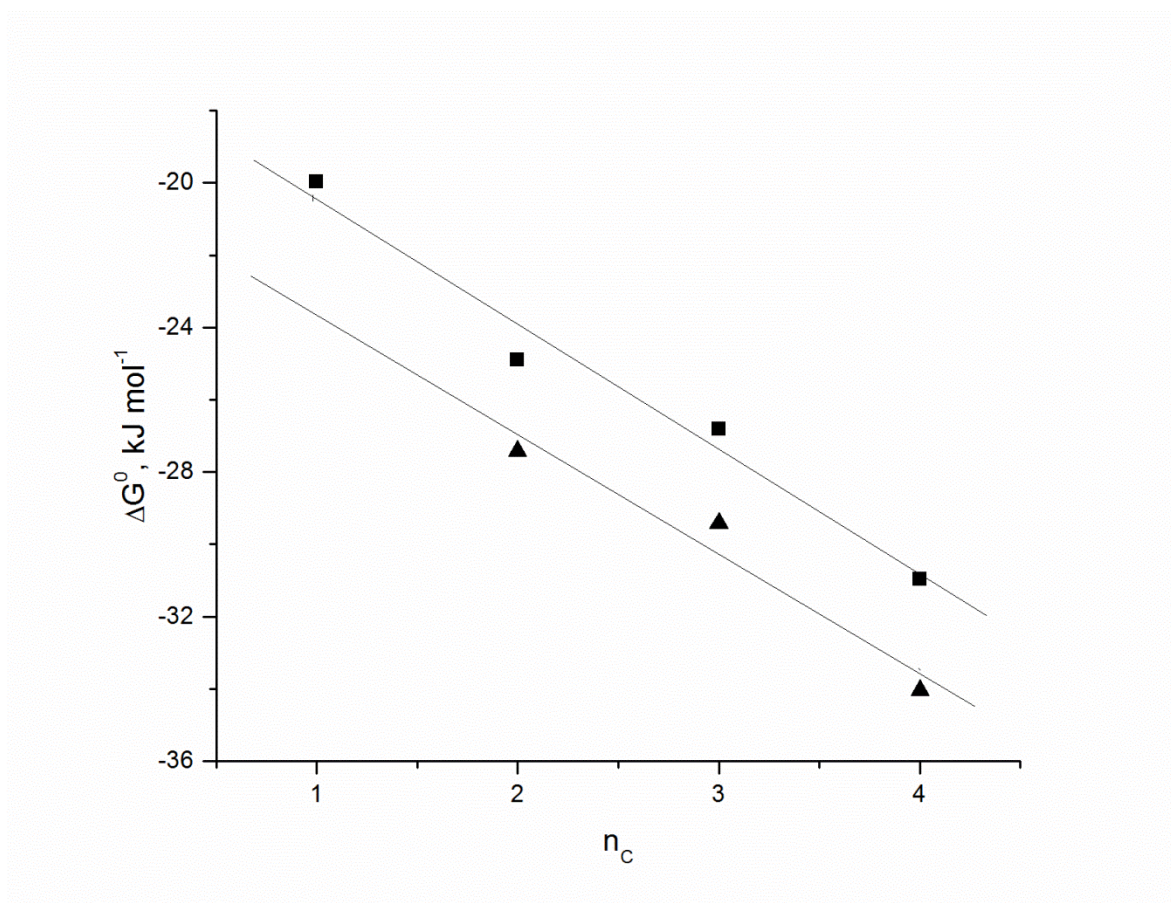
Figure 7. Standard free energy of transfer of p-alkyl phenols from water to polymer aggregates ($\Delta\mu^0_t$), as a function of the number of carbon atoms on the alkyl chain. HPG_{17} (■) and HPG_4-RBr_{13} (▲).

The slopes are similar and the incremental free energy per methylene group, $\Delta\mu^0_C$, is −3.50 and −3.30 kJ mol^{-1} for HPG_{17} and HPG_4-RBr_{13}, respectively, and agree well with that determined for transfer of methylene group from water to heptane (−3.27 kJ mol^{-1}). These results suggest that alkyl chains have similar locations in both aggregates. On the other hand, the free energies of transfer of the phenol moiety from water into polymer aggregates, $\Delta\mu^0_{Ph}$, obtained from the intercept are −16.9 and −20.4 kJ mol^{-1} for HPG_{17} and HPG_4-RBr_{13}, respectively. The values of $\Delta\mu^0_{Ph}$ are larger than those of $\Delta\mu^0_C$, which indicate that

the location of p-alkylphenols in the aggregates formed by dendritic polymers is mainly determined by the transfer of the phenol moiety to the hydrophobic core. Interestingly, the value of $\Delta\mu^0_{Ph}$ measured for HPG is much lower than those measured in other polymer and SDS micelles [25,40]. This indicates that phenols in PG_{17} aggregates are located in a more polar environment than that provided by normal micelles. This conclusion is in line with fluorescence probing results indicating that water molecules enter freely into the HPG_{17} aggregate core.

4. Conclusions

A low molecular hyperbranched polyglycidol and its ester derivative were synthesized and characterized following standard procedures. The results indicate that a HPG with 17 units and a branching degree of 0.41 was obtained. The esterification of HPG_{17} gives HPG_4-RBr_{13}, i.e. an ester with 78% of the hydroxyl groups converted into RBr. These two HPG have different polarity and therefore it is expected that their aggregation behavior should be also different. The formation of multimolecular aggregates was monitored by fluorescence probing using pyrene as probe, and the measured CAC values are 2.5 mM and 0.25 mM for HPG_{17} and HPG_4-RBr_{13}, respectively. The size and size distribution of the formed aggregates were determined by DLS. At low concentrations of HPG aggregates of 3.5 nm and 22 nm were observed, whereas at concentrations above the CAC larger aggregates are observed for both HPG. In the whole range of concentrations these aggregates are able to solubilize pyrene. Above the CAC the solubilization of p-alkylphenols shifts the size distribution to larger sizes and induces the disappearance of the smaller aggregates.

The partition coefficients of p-alkylphenols and the standard free energy of transfer from the aqueous phase to the pseudo-micellar phase were determined for both polymers at concentrations well above the CAC. The results show that K_X increases with increasing

length of the side alkyl chain, and are larger for HPG_4-RBr_{13} micelles than for HPG_{17}

micelles. The free energy values are negative and can be separated in contributions from

the phenol constitutive groups. The location into the aggregate and amount of transfer is

determined mainly by the phenolic ring.

Acknowledgements

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