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Synthesis and aqueous solution properties of aliphatic double chain end-capped poly(ethylene glycol)

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Summary

A PEG-based amphiphilic polymer bearing two aliphatic double chain moieties was prepared. Its diluted aqueous solution properties were studied by viscometry, dye solubilization and rheology. At concentrations lower than (6-8)x10^{-3} g/mL ring-shaped macromolecules were formed due to intrachain hydrophobic interactions. At concentrations about (6-8)x10^{-3} g/mL a formation of "flower" type aggregates took place. 1,6-Diphenyl-1,3,5-hexatriene solubilization was used to prove the existence of hydrophobic domains and a critical aggregation concentration of 7x10^{-3} g/mL was determined. The peculiar viscosity profile and the rheopectic behavior of the amphiphilic polymer were attributed to the existence of aggregates and to a temporary network formation during deformation, respectively.

Introduction

The water soluble associative polymers have attracted widespread attention due to their wide application both in the industry and for basic research. Most of the conventional associative polymers, e.g., hydrophobically modified ethoxylated urethans (HEUR), however, are polydisperse compounds with a multimodal molecular weight distribution. This makes it difficult to interpret the associative behavior of such polymers. Therefore, model polymers of low polydispersity have been prepared. These are linear water soluble polymers, normally poly(ethylene glycols) (PEGs), with hydrophobic end groups attached via ether, ester, or urethane [1-4] linkages. Studies on aqueous solutions of these hydrophobically end-capped PEGs using techniques such as SANS, SAXS, fluorescence, light scattering, NMR relaxation, and ESR measurements [1,4-11] have been carried out. It has been found that at low concentrations the two hydrophobic end groups associate in water to form "flower" type micelles similarly to the poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide) triblock copolymers in aqueous solution [12].
The low immunogenicity of PEGs makes them attractive polymers for biomedical applications [13]. Hydrophobically modified PEGs, called also PEG-surfactants or PEO-lipids, consisting of a hydrophilic PEG chain covalently attached to a hydrophobic aliphatic double chain moiety have been prepared [14-17]. These

amphiphilic polymers are able to interact with lipid bilayers - a property widely employed for the preparation of PEG-coated liposomes [15,18-21] and bioactive gels with enhanced mechanical stability [14,22]. The synthesis of amphiphilic polymers consisting of double chain hydrophobic moieties attached to the two ends of a PEG chain has been described as well [23]. The hydrophobic moieties comprising 3,4-(dialkoxy)benzoic acid residues are attached to the PEG chains via ester linkages. These macromolecules interact with lipid bilayers adopting either looping or cross-bridging conformations.
In this paper we report the synthesis of an associative polymer bearing aliphatic double chain moieties. α,ω-Dihydroxy PEG (M_w = 20000) is end-capped with this moiety thus making ABA type linear associative polymer, where A and B represent an aliphatic double chain and a PEG chain, respectively. The chemical structure of the associative polymer is given in fig. 1.

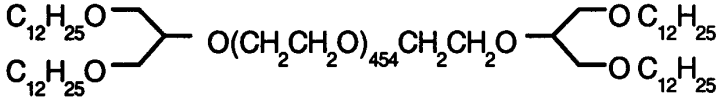

Fig. 1 Chemical structure of the PEG-based amphiphilic polymer used in this study.

The major differences between some of the previous studies and the current work are the structures of the aliphatic double chain moieties and the polymer architecture. In contrast to the AB and ABA type PEG-surfactants bearing 3,4-(dialkoxy)benzoic acid residues, described elsewhere [14,23], the double chain moiety of the present amphiphilic polymer consists of a glycerol skeleton bearing two dodecyl chains. This structure is very similar to that one found in the naturally occurring membrane forming agents, e.g., phospholipids. On the other hand the PEG molecular weight and the ABA type architecture differ from those ones of PEO-lipids [15]. Aqueous solution properties of this new amphiphilic polymer (hereinafter $(didodecyl)_2$PEG20K) at low concentrations are investigated by viscometry, dye solubilization and rheology

Experimental

Materials

All solvents and reagents were supplied by Fluka or Aldrich. The solvents were purified by standard methods, whereas the reagents were used as received. Poly(ethylene glycol) (Aldrich) with a weight average molecular weight of 20000 g/mol and a polydispersity of 1.05 was used.

Synthesis of 1,3-didodecyloxy-glyceryl-2-toluene sulfonate

In a two-necked, round-bottom flask, equipped with a stirrer 4 g ($9.4x10^{-3}$ mol) of 1,3-didodecyloxy-propane-2-ol, prepared according to procedures described elsewhere

[24] were dissolved in 20 mL of freshly distilled pyridine. 2.3 g ($12.1x10^{-3}$ mol) of p-toluenesulfonyl chloride were added to the solution. The mixture was stirred for 48 hours at a temperature below 15 °C. Afterwards the mixture was poured into 200 mL of ice-water, the crystals formed were collected on a Buchner funnel and washed several times with water. The product was re-crystallized twice from petroleum ether. ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 6H, $-CH_2-O-CH_2-CH_2-(CH_2)_9-C\underline{H}_3$); 1.26 (m, 36H, $-CH_2-O-CH_2-CH_2-(C\underline{H}_2)_9-CH_3$); 1.44 (m, 4H, $-CH_2-O-CH_2-C\underline{H}_2-(CH_2)_9-CH_3$); 2.44 (s, 3H, $C_6H_4-C\underline{H}_3$); 3.33 (m, 4H, $-CH_2-O-C\underline{H}_2-CH_2-(CH_2)_9-CH_3$); 3.57 (d, 4H, $-C\underline{H}_2-O-CH_2-CH_2-(CH_2)_9-CH_3$); 4.66 (q, 1H, $-(CH_2)-C\underline{H}-SO_3$); 7.32 (d, 2H, $-C_6H_4-CH_3$); 7.82 (d, 2H, $-SO_3-C_6H_4$). Elemental analysis (%): C, 70.10 (found 69.98); H, 10.65 (found 10.73); O, 13.75 (found 13.42); S, 5.50 (found 5.39). Yield 78 %.

End-capping of PEG 20000

The reaction between 0.307 g ($5.28x10^{-4}$ Mol) of 1,3-didodecyloxy-glyceryl-2-toluene sulfonate and 4.4 g ($2.2x10^{-4}$ mol) of α,ω-dihydroxy PEG 20000 previously metalled by potassium naphtalide was carried out in 60 mL of dry tetrahydrofurane at reflux for 48 hours. Then tetrahydrofurane was removed under reduced pressure and the residue was dissolved in methylene chloride. The insoluble material was removed by centrifugation. The hydrophobically modified PEG was isolated by precipitation in hexane. The product was washed with portions of 20 mL of hexane until no more hexane-soluble fraction was extracted. 4.27 g of a white solid was isolated and dried in vacuo up to a constant weight. The degree of substitution of the hydroxyl groups determined by ^{1}H NMR in DMSO was found to be 100 %. The result was confirmed by determination of the residual hydroxyl groups by UV spectroscopy after a reaction with phenyl isocyanate.

Nuclear Magnetic Resonance (NMR)

^{1}H NMR spectra were recorded at 250 MHz on a Bruker 250 spectrometer. The samples were prepared as solutions in $CDCl_3$ or DMSO. The chemical shifts are given in ppm from tetramethylsilane. All spectra were recorded at 25 °C.

Viscometry

The viscosity measurements were carried out with Ubbelohde type viscometer equipped with a capillary of 0.45 mm diameter. The solvent (water) and solutions were filtered prior to any measurements. The apparatus was thermostated at 25 °C

Dye solubilization

A number of aqueous solutions of $(didodecyl)_2$PEG20K in the concentration range from $0.1x10^{-3}$ to $80.0x10^{-3}$ g/mL were prepared. 25 µL of a 0.4 mM solution of 1,6-diphenyl-1,3,5-hexatriene (DPH) in methanol were added to each 2.5 mL of the copolymer solution. Solutions were incubated in dark for 16 hours. The absorbance spectra in the range λ = 300 - 500 nm were recorded on a *Specord UV-vis* spectrometer (*Carl Zeiss, Jena*). The main absorption intensity peak, characteristic of DPH solubilized in a hydrophobic environment, was at 356 nm. The measurements

were done at a room temperature.

Rheological measurements

Rheological measurements were conducted using a *Brabender Rheotron* 1.8 rheometer. A P_7/B system with cone-plate geometry (cone diameter 50 mm, plate diameter 52 mm, cone angle 0.3°) working at shear rates from 0.1 to 100 s^{-1}, was used for rheological measurements of $10x10^{-3}$ g/mL aqueous solutions. The measurements were done at a room temperature.

Results and discussion

The variations of the reduced viscosities, η_{red}, of $(didodecyl)_2$PEG20K and of its unmodified PEG 20000 (PEG20K) analogue in dilute aqueous solutions are shown in fig. 2.

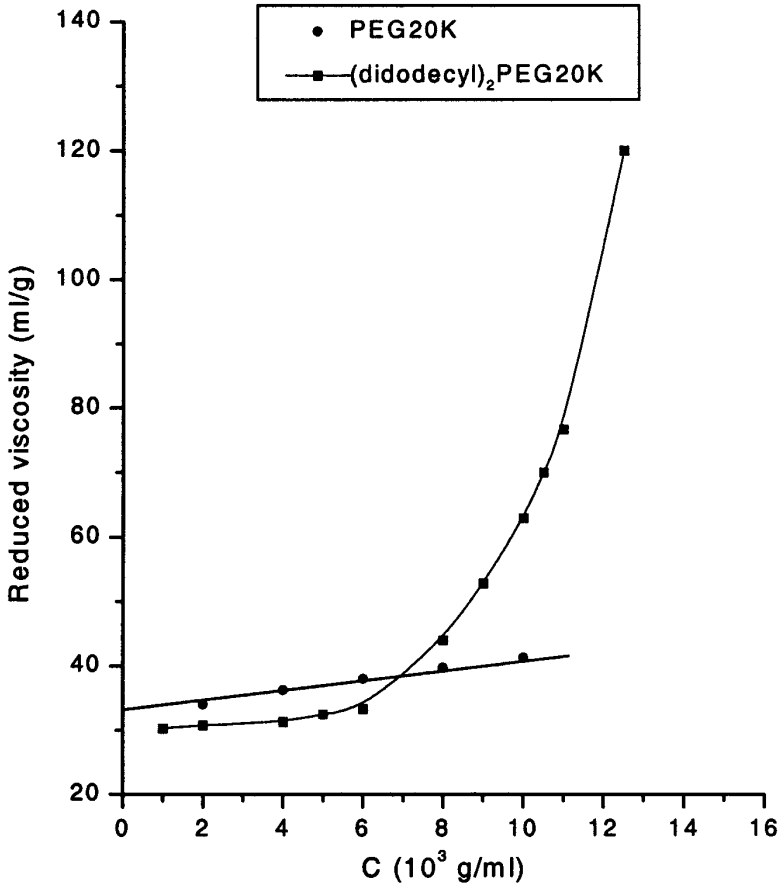

Fig. 2 Variation of the reduced viscosity of PEG20K and $(didodecyl)_2$PEG20K as a function of concentration in aqueous solutions at 25 °C. Symbols are defined in the inset table.

The concentration dependence of η_{red} of PEG20K was linear and gave an intercept, corresponding to the limiting viscosity of 33.1 mL/g. In contrast to PEG20K, the concentration dependence of η_{red} of $(didodecyl)_2$PEG20K was not linear: at low concentrations its viscosity was lower than that of PEG20K, whereas at concentrations

higher than (6-8)x10^{-3} g/mL it gradually increased. Such a behavior could be explained by assuming that at low concentrations ring-shaped macromolecules were formed due to intrachain interactions. This type macromolecules have smaller dimensions than the linear ones at equal molecular weights [25,26]. At higher concentrations (6-8x10^{-3} g/mL) a formation of polymolecular aggregates took place. The aggregates were assumed to consist of a hydrophobic interior surrounded by a hydrophilic corona built up of PEG chains in a looping conformation. Upon a further increase of the concentration the viscosity increased due to bridging interactions between aggregates.

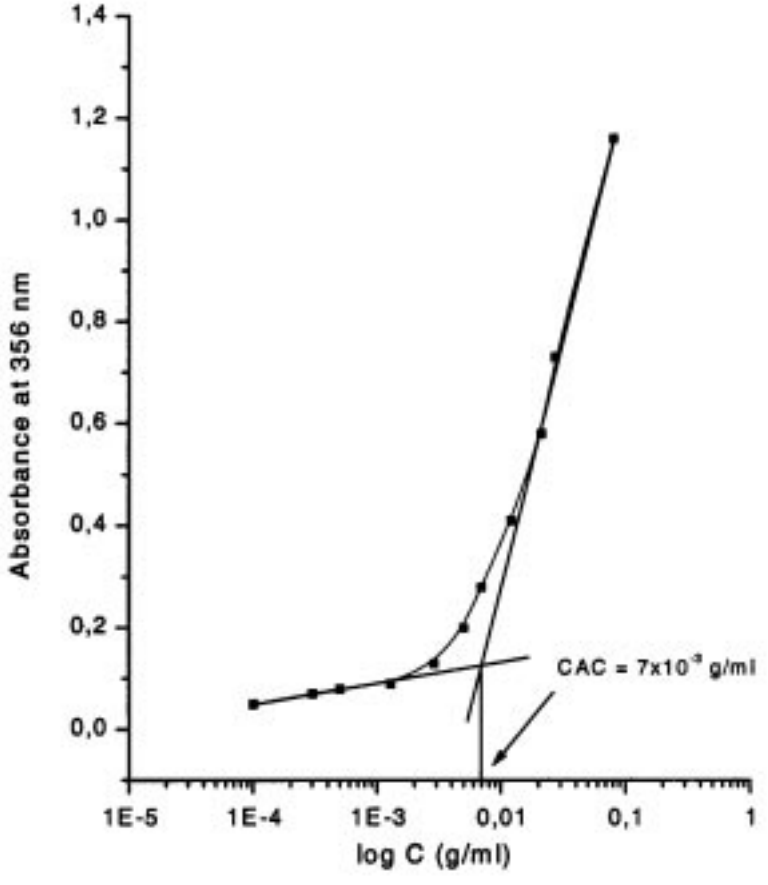

Fig. 3 Variation of the absorbance of DPH at 356 nm as a function of $(didodecyl)_2$PEG20K concentration in aqueous solution.

A dye solubilization method was used to prove the existence of hydrophobic domains. DPH was a probe molecule. DPH solubilization has been used previously for the determination of the critical aggregation concentration of nonionic amphiphiles [24,27,28]. A typical plot of DPH absorbance at 356 nm versus log $(didodecyl)_2$PEG20K concentration is presented in fig. 3. A critical aggregation concentration of 7x10^{-3} g/mL, was determined. The value fits very well the onset of the viscosity increase.

The rheological properties of 10x10^{-3} g/mL aqueous solutions of $(didodecyl)_2$PEG20K and the reference PEG20K were studied as well. This concentration is slightly higher than the critical aggregation concentration of $(didodecyl)_2$PEG20K but still lower than the overlap concentration of PEG20K, defined as $C^* = 1/[\eta]$. Fig. 4 shows their steady

shear viscosities as a function of shear rate. Different viscosity profiles were observed. The viscosity profile of (didodecyl)$_2$PEG20K is indicative for the larger resistance of the system to deformation. Even at the highest shear rates, the shear viscosity of the (didodecyl)$_2$PEG20K solution is still greater than that of the solution of the reference PEG20K. In addition the zero shear viscosity of the modified polymer was an order of magnitude higher than that of PEG20K. The associative interactions are believed to be responsible for the enhanced thickening, and generally, for the different behavior of the polymer species in aqueous solution.

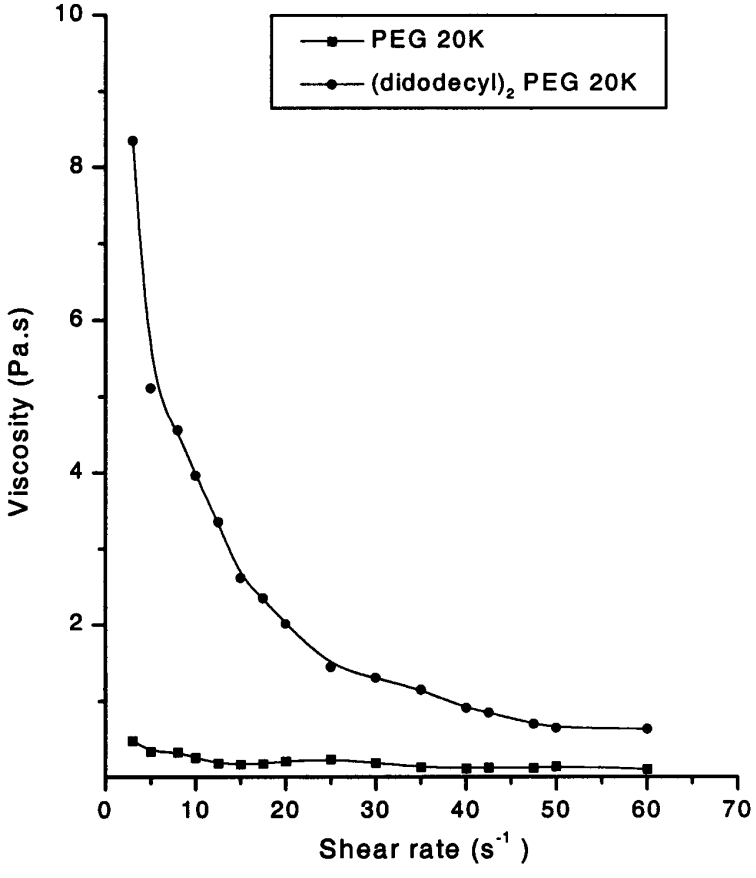

Fig. 4 Viscosity as a function of shear rate for 10x10^{-3} g/mL aqueous solution of PEG20K and (didodecyl)$_2$PEG20K. Symbols are defined in the inset table

The solutions behaved differently when a standard thixotropy test [29] was carried out. It was found that the PEG20K solution was thixotropic, whereas the aqueous solution of (didodecyl)$_2$PEG20K showed rheopexy (fig. 5). The rheopectic behavior of (didodecyl)$_2$PEG20K finds its explanation in terms of a structure formation during deformation. The shearing of the "flower" type aggregates of (didodecyl)$_2$PEG20K is expected to lead to streching of the aggregates. As a result some of the hydrophobic ends no longer reside in the cores of the aggregates. They anchor in other aggregates thus promoting a temporary network formation. Thus, the rheopectic behavior is related to a transition to interaggregate bridging associations. It should be emphasized, however, that rheopexy is a history-dependent property and an unambiguous interpretation of these results is not possible at present.

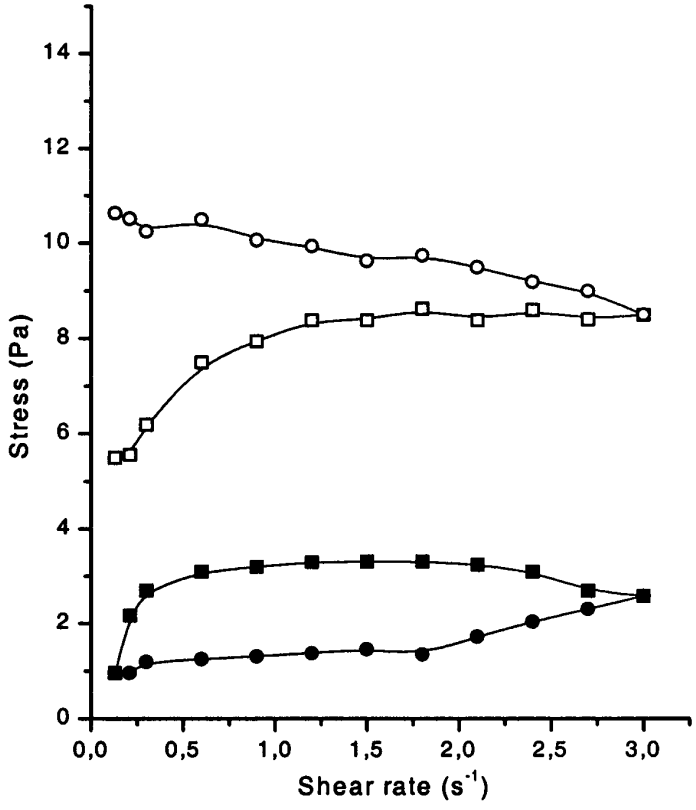

Fig. 5 A thixotropy/rheopexy test presented as a shear stress against shear rate plot of $10x10^{-3}$ g/mL aqueous solutions of PEG20K (filled symbols) and $(didodecyl)_2$PEG20K (open symbols). Scan completed in 60 s; squares -increasing shear rate curve; circles - decreasing shear rate curve

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