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Phase diagram of tyloxapol and water – II

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Summary

The phase diagram of mixtures of tyloxapol, a nonionic liquid polymer of the alkyl aryl polyether alcohol type, and water and the corresponding liquid crystalline phases have been investigated by X-ray scattering. Below 35 wt% tyloxapol micellar solutions are formed. At 3 wt% they contain spherical micelles with a diameter around 7 nm. Increasing concentrations give rise to interparticle interactions that are clearly observable above 10 wt%. Complementary viscosity measurements indicate a pronounced hydration of the polyoxyethylene chains. From 37.5 to 65 wt% there is a lyotropic liquid crystalline hexagonal phase (middle phase, M_1 phase). Its lattice parameter increases nearly linearly with water concentration but is almost independent of temperature. There are no transitions of the hexagonal phases to thermotropic liquid crystalline phases at temperatures between 20 and 65°C. At 65°C all systems exhibit two broad diffuse reflections with a spacing ratio of 1 : 1/2. At all concentrations, samples heated to 65°C and cooled to room temperature return to the hexagonal phase. The X-ray data confirm the existence of a cubic phase in a narrow concentration range around 70 wt% below 30°C. Its three-dimensional structure, however, could not be determined from the eight reflections in the scattering pattern. Retransformation of the cubic phase from the melt is highly retarded. On cooling, the cubic phase which is closest to the hexagonal phase at 20°C forms a metastable hexagonal intermediate phase with a small lattice parameter. The melts of cubic phases which exist in the vicinity of the lamellar phase region form an intermediate lamellar phase. Between 74 and 80 wt% at room temperature there is a liquid crystalline lamellar phase. The reflections of the thermally unstressed samples are weak compared with the sharp reflections observed after cooling of molten samples. The melts of all three liquid crystalline phases are viscous liquids. Their scattering patterns display two broad maxima with spacings progressively decreasing from 5.3 to 4.6 nm and from 2.7 to 2.4 nm as the concentration increases from 37.5 to 77.5 wt%. No liquid crystalline phases were observed for the binary mixtures containing more than 80 wt% but these highly viscous liquids display a broad maximum around 4.2 nm.

Introduction

Tyloxapol, described as a nonionic liquid polymer of the alkyl aryl polyether alcohol type in the official monographs of the US Pharmacopeia (USP XXII, 1990), is a nonionic surfactant with detergent properties (Lewis, 1981). The phase diagram of tyloxapol/water mixtures was established between 20 and 65°C (see Fig. 6 of preceding article (Westesen, 1994)). At room temperature, three liquid crystalline phases were found: a lamellar phase (neat phase or G phase (Fontell,

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1974)), a cubic phase and a hexagonal phase (middle phase or M_1 phase (Fontell, 1974)). These phases were characterized by polarized light microscopy and transmission electron microscopy (TEM) of replicas of freeze-fractured samples and their thermal properties were studied by differential scanning calorimetry (DSC) and hot-stage polarized light microscopy. As none of these methods allows a rapid systematic quantitative characterization of the supramolecular structures and their underlying molecular order and temperature dependence, synchrotron radiation X-ray scattering was used to investigate the complete phase diagram. Complementary information on the properties of the micellar systems was obtained by viscometry.

Materials and Methods

Materials

Tyloxapol USP (Sterling Organics), sodium chloride (analytical grade; Merck) and bidistilled water were used.

Preparation of binary tyloxapol / water systems

Tyloxapol / water systems were prepared as described previously (Westesen, 1994).

Determination of density

The density of aqueous systems was determined at 20.0°C with a DMA 48 density meter (Anton Paar, Graz, Austria).

Synchrotron radiation X-ray scattering (SRSAXS)

Measurements were performed on the double focussing monochromator mirror camera X33 (Koch and Bordas, 1983) of the EMBL in HASYLAB on the storage ring DORIS of the Deutsches Elektronen Synchrotron (DESY) using a linear delay line readout detector (Gabriel and Dauvergne, 1982) and the standard data acquisition and evaluation systems (Boulin et al., 1986, 1988). In some cases, a film was placed on the detector to check that the scattering was isotropic.

The observation range was $0.038 < s < 0.613$ nm^{-1} for micellar systems and $0.038 < s < 1.699$ nm^{-1} for liquid crystalline systems, where $s = 2 \sin \theta/\lambda$, 2θ is the scattering angle and λ the wavelength (0.15 nm).

The samples were filled in thermostated cells. For time-resolved measurements they were first heated from 20 to 37°C, then from 37 to 45°C, from 45 to 65°C and finally cooled from 65 to 20°C. The X-ray patterns were recorded in three separate 1 min time frames to monitor radiation damage and beam stability. For the micellar systems the scattering of the dispersion media was also measured. Data reduction, background subtraction and correction for detector response were performed following standard procedures (see, e.g., Koch (1991)) using the program SAPOKO (Svergun and Koch, unpublished). The distance distribution of the micellar systems were calculated using the indirect transform program GNOMOKO (Svergun et al., 1988; Svergun, 1992).

Viscometry

The viscosity of a series of aqueous systems (tyloxapol concentration: 0.1–1.5 in steps of 0.1, 2.0, 2.5, 3.0, 4.0, 5.0, 6.5, 8.0, 10.0, 15.0% w/w) was determined. In addition, the viscosities of two series (tyloxapol concentration 0.1–1.3 in steps of 0.1%) containing 0.04 and 0.14 mol sodium chloride were determined. The kinematic viscosities were determined from the efflux times (t_{efflux}) with an Ubbelohde capillary viscometer ASTM (ASTM D 2515, Schott Geräte, Germany) at 20.00°C. During the course of any single measurement the mean temperature of the water bath (Lauda Ultra Thermostat D60 with Lauda Simplex Pump S15/22/6, Julabo FP40-HC prethermostat, resistance bridge model F 16, precision temperature controller model 300 and Heraeus PT12 resistance thermometer (100 Ω)) did not vary by more than 0.003°C. Timing was accomplished manually (Profil II-Stopstar, Hanhart) with a precision of 1×10^{-3}% on the efflux times displayed on the stopwatch. The viscometer was calibrated with two Newtonian reference liquids for viscometry of the Physikalisch Technische Bundesanstalt, Germany (code 1A and 1B) at 20.00°C immediately before the measurements on

the micellar systems. The dynamic viscosities (η_{dyn}) were calculated as:

$$\eta_{dyn} = \eta_{kin} \cdot \rho \quad (1)$$

where η_{kin} is the kinetic viscosity ($t_{efflux} \cdot c$), c denotes the constant of the viscometer ($c = 2.756 \times 10^{-3}$), and ρ is the density of the tyloxapol-water mixture. The observed efflux times were not corrected for surface-tension effects (see Results).

Surface tension

The surface tension was measured at 20.3°C with an interfacial tensiometer (Kruess Processor Tensiometer K12, Germany) equipped with a sand blasted platinum Wilhelmy plate (19.9×0.1 mm^2). An aqueous stock solution of tyloxapol (28.87 wt%) was prepared and added in steps to a sample of 20.0 ml bidistilled water to obtain concentrations from 0.1 to 1.0% in steps of 0.1% and 1.25 to 2.5% in steps of 0.25%. Measurements were taken after an equilibration period of 30 min after addition of the stock solution. The surface tension corresponds to the first measurement immediately after equilibration. In addition, nine subsequent measurements were performed on each sample at time intervals of 10 s but without allowing the Wilhelmy plate to detach from the surface of the liquid. These values exhibited variations of less than 0.02 mN/m from the first value for the aged surface and were slightly lower in most cases.

Results

Synchrotron radiation X-ray scattering

Lyotropic and thermotropic liquid crystalline phases of amphiphiles can be distinguished by their characteristic spacings (Fontell, 1974) and the corresponding values for the tyloxapol/water systems as a function of concentration and temperature are given in Table 1.

At room temperature there are an extended hexagonal region, a narrow cubic phase and a lamellar phase.

The d spacing of the innermost reflection of the hexagonal phase which is directly related to the lattice parameter a ($a = 2d/\sqrt{3}$) decreases almost linearly with increasing tyloxapol concentration. To check for possible orientation effects some patterns were also recorded on film, but such effects were not found. The hexagonal phases are the most temperature resistant lyotropic liquid crystalline phases in the phase diagram. They still exist between 37 and 45°C and their Bragg spacings change only slightly with increasing temperature. On liquefaction the systems display two broad reflections with spacings around 5.0 and 2.5 nm (Table 1). The maximum d value of the liquefied systems has a nearly parabolic dependence on concentration (d in nm):

$$y = 1.4194 + 0.15774x - 0.0015184x^2 \ (R^2 = 0.951) \quad (2)$$

The liquid crystal/liquid transition temperature is below 65°C in all cases. For the hexagonal phases the liquid crystal/liquid transition temperature is the lowest for systems which are close to the phase boundaries, e.g., systems containing 37.5 or 65 wt% tyloxapol (Table 1). Hexagonal systems between 50 and 60 wt% have approximately the same d values before and after liquefaction, indicating a rapidly reversible equilibrium. In contrast, liquefaction of the 37.5 and 40 wt% systems results in a large decrease of the lattice parameter, indicating the formation of an intermediate hexagonal structure. The decrease in lattice parameter of the systems around 40 wt% is due to the exclusion of water and the formation of water droplets can be directly observed under the polarizing microscope. Heating of the 40 wt% system to 45°C (i.e., below the melting point) and cooling to room temperature did not significantly alter the lattice parameter of the system returned to room temperature.

Between 67.5 and 72.5 wt% tyloxapol there is a cubic phase in a narrow concentration range below 30°C giving rise to eight reflections with characteristic spacing ratios (Table 1 and Fig. 1) but which do not suffice to determine the three-dimensional structure.

The maximum d values of the lyotropic liquid crystalline lamellar phases may slightly decrease ($\cong 0.1$ nm) with decreasing water content. These lamellar phases already exhibit two broad reflections at 37°C (Table 1). For systems around 75 wt% polarizing microscopy suggests the coexistence of a lamellar liquid crystalline phase and a dispersed optically isotropic phase. The X-ray data indicate that the latter is amorphous. In addition, the existence of what appears like small crystals dispersed in the lamellar phase at 77.5% system could not be confirmed by X-ray scattering as there were no sharp reflections in the X-ray patterns.

The shapes of the reflections in the X-ray patterns of all liquid crystalline samples have been compared before and after the temperature scans to 65°C and back to room temperature. At 65°C all systems are liquid but two broad scattering maxima with an approximate spacing ratio of 1 : 1/2 can still be observed for the 70 wt% system as illustrated in Fig. 1 and Table 1. Within minutes after cooling to room temperature the reflections of the hexagonal and lamellar phases reappear. They are, however, sharper and more intense than before the temperature scans. The phenomenon is especially pronounced for the liquid crystalline lamellar phases.

In contrast, the retransformation of the liquid crystalline cubic phases from the liquid systems is highly retarded for the 70% system. Below 70 wt% an intermediate hexagonal phase (Table 1) is detected whereas above 70 wt% there is an intermediate lamellar phase (Table 1). The maxi-

TABLE 1

Spacings (d values) in nm for binary tyloxapol / water mixtures as a function of tyloxapol concentration (wt%) at 20, 37, 45, 65°C and back to 20°C

wt%	20°C	37°C	45°C	65°C	20°C
3	7				
20	8.6 3.7				
30	7.3 3.6				
35	6.7 3.4				
37.5	6.1 3.5 3.0	6.2 3.5 3.1	7.0 3.4	5.2 [a] 2.7 [a]	5.0 2.9 2.5
40	5.9 3.4 2.9	6.0 3.4 3.0	6.3 3.5 3.0	5.3 [a] 2.8 [a]	5.1 2.9 2.5
50	5.4 3.1 2.7 2.0	5.5 3.1 2.7	5.6 3.2 2.8 2.0		5.5 3.1 2.7 2.0
60	5.0 2.9 2.5	5.0 2.9 2.5	5.2 2.9 2.6	5.4 [a] 2.7 [a]	5.1 2.9 2.5 1.9
62.5	4.9 2.8 2.5	5.0 2.9 2.5	5.1 2.9 2.5	5.3 [a] 2.7 [a]	5.1 2.9 2.5 1.9
65	4.9 2.8 2.4	4.9 2.8 2.4	5.0 [a] 2.6 [a]	5.4 [a] 2.7 [a]	4.9 2.8 2.4
67.5	5.0 4.3 3.3 3.1 2.7 2.6 2.5 2.4	5.0 [a] 2.5 [a]	5.0 [a] 2.6 [a]	5.1 [a] 2.6 [a]	4.8 2.7 2.4
70	5.0 4.3 3.2 3.1 2.7 2.6 2.5 2.4	4.8 [a] 2.5 [a]	4.9 [a] 2.5 [a]	5.0 [a] 2.6 [a]	4.9 [a] 2.5 [a]
72.5	4.8 4.2 3.1 3.0 2.6 2.5 2.4 2.3	4.8 [a] 2.5 [a]	4.8 [a] 2.5 [a]	4.8 [a] 2.5 [a]	4.8 2.4
75	4.8 2.4	4.8 [a] 2.4 [a]	4.8 [a] 2.4 [a]	4.8 [a] 2.5 [a]	4.8 2.4
77.5	4.7 2.3	4.6 [a] 2.4 [a]	4.6 [a] 2.4 [a]	4.5 [a] 2.5 [a]	4.7 2.3
80	4.6 [a] 2.4 [a]	4.6 [a] 2.4 [a]	4.5 [a] 2.4 [a]		
90	4.2 [a]	4.1 [a]	4.1 [a]		
97	4.3 [a] 3.7 [a] 1.4 [a]	4.3 [a] 3.7 [a] 1.4 [a]	4.3 [a] 3.7 [a] 1.8 [a]		

[a] Broad, diffuse reflections.

mum d value of the intermediate hexagonal phase is different from that of the most temperature resistant hexagonal systems but close to that of the hexagonal system near the upper phase boundary (Table 1).

Systems containing less than 35 wt% tyloxapol are isotropic liquids. The scattering curve of a system containing 3 wt% (Fig. 2) is characteristic of spherical micelles with a diameter around 7 nm as derived from the corresponding distance distribution function $p_{(r)}$. The scattering curves of the aqueous systems containing between 10 and 35 wt% tyloxapol in Fig. 2 display strong interparticle interferences.

In the polarized light microscope all binary systems above 75 wt% also contain what appears like small crystals although no sharp reflections characteristic of dispersed crystalline material

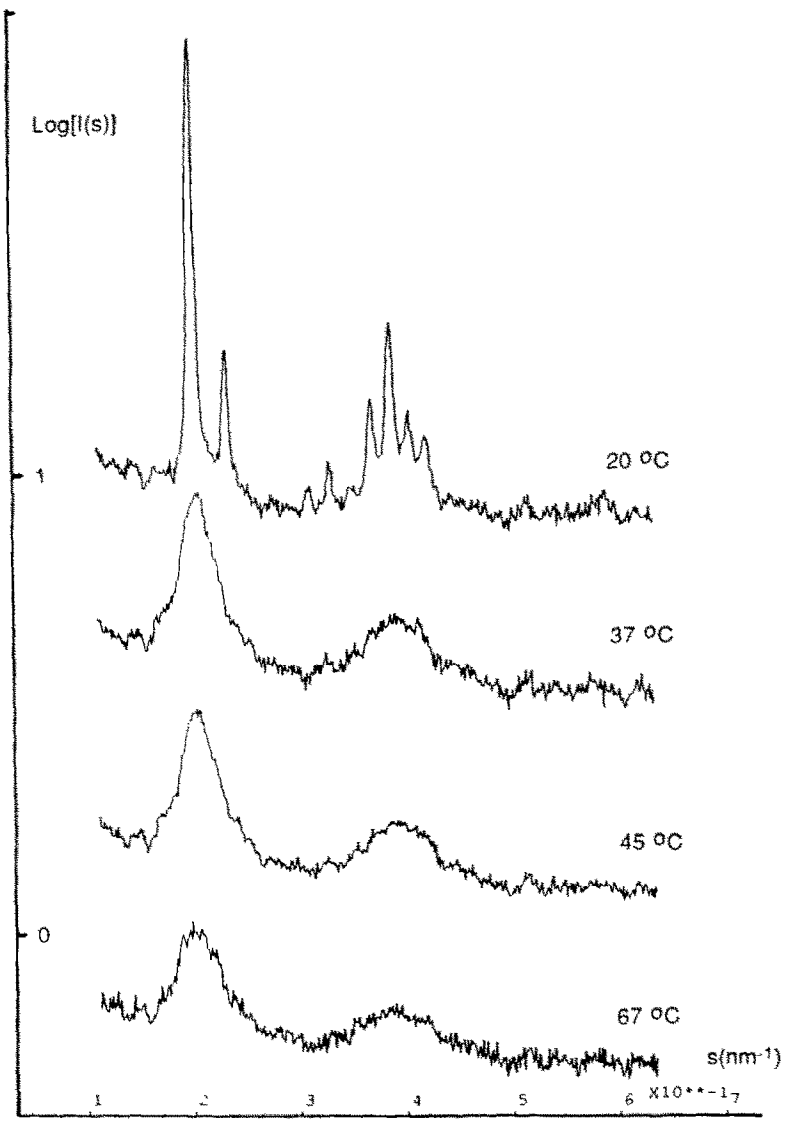

Fig. 1. X-ray scattering pattern of the system containing 70 wt% tyloxapol at different temperatures. The curves have been displaced for better visualization.

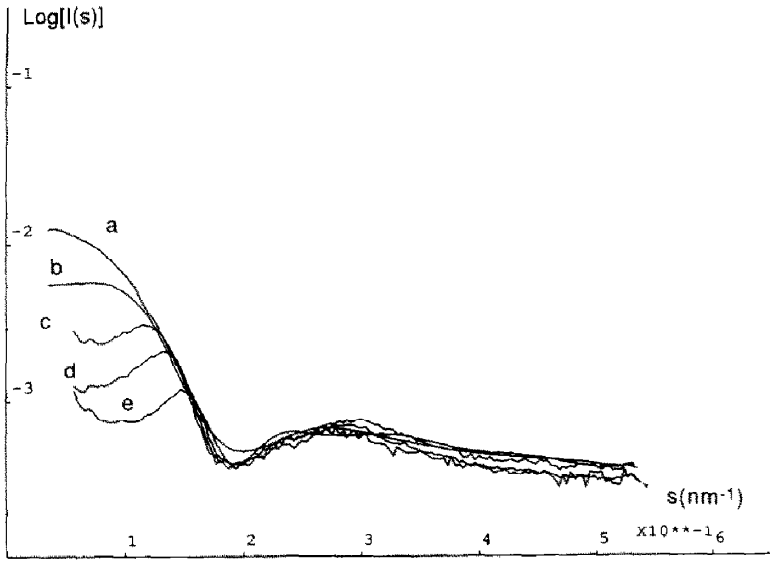

Fig. 2. X-ray scattering patterns of micellar systems containing 3% (a), 10% (b), 20% (c), 30% (d) and 35 wt% tyloxapol (e).

could be observed in the X-ray scattering pattern. At concentrations above 80 wt%, there are also no liquid crystalline phases but the maxima in the X-ray scattering patterns of these highly viscous liquids become broader and weaker at higher temperatures (Fig. 3).

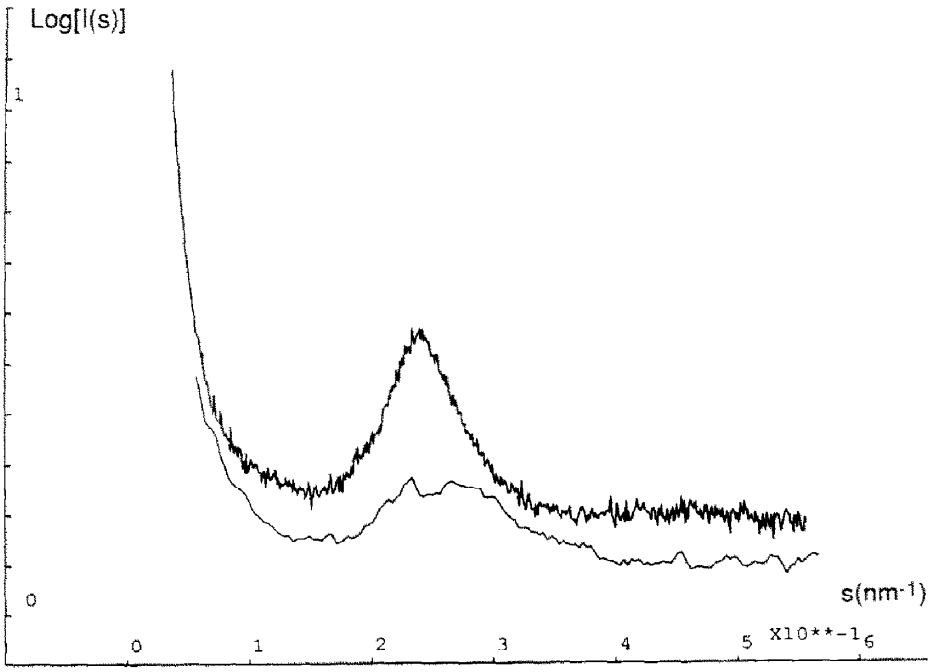

Fig. 3. X-ray scattering patterns of systems containing 90 wt% tyloxapol (top) and 97 wt% tyloxapol (bottom). The curves have been displaced for better visualization.

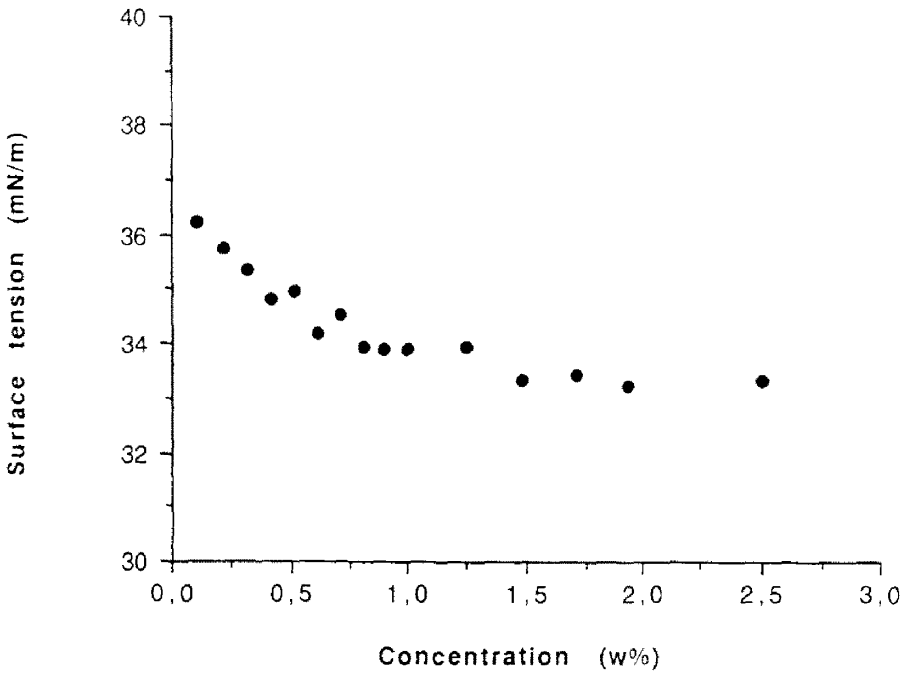

Fig. 4. Surface tension vs concentration curve of aqueous systems in the concentration range from 0 to 2.5% (g/ml).

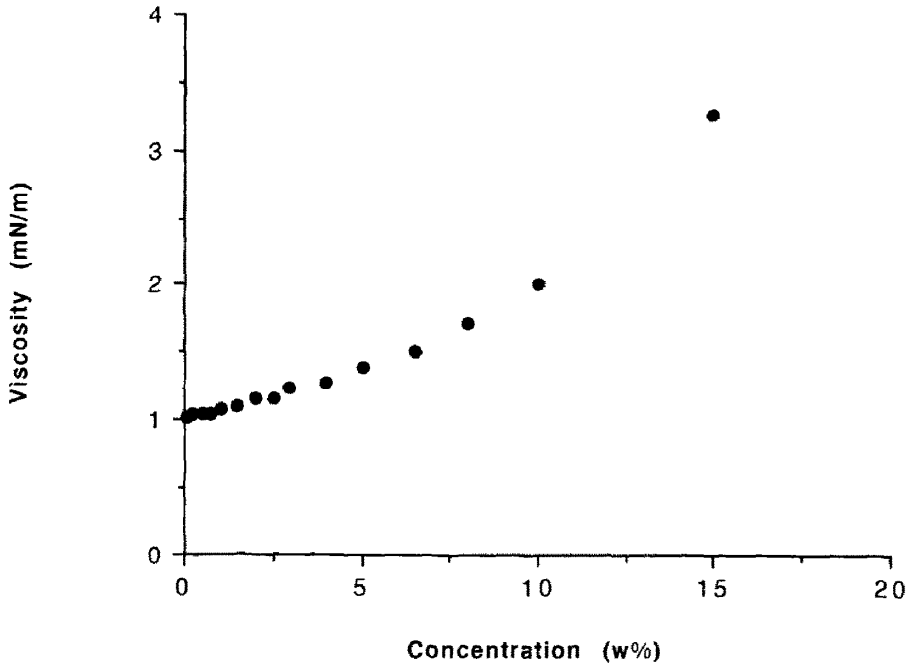

Fig. 5. Viscosity vs concentration curve of aqueous micellar systems in the concentration range from 0.25 to 15% (g/ml).

Surface tension

The results of the surface tension measurements are shown in Fig. 4. The surface tension (σ) decreases exponentially with increasing tyloxapol concentration and levels off around 33.3 mN/m. The surface tension of the 0.1% system ($\rho_{20} = 0.9983$ g/ml) is 36.2 mN/m or half the value found for bidistilled water (72.4 mN/m). The surface tension of the two Newtonian reference liquids for viscometry is 26.2 mN/m for reference liquid 1A ($\rho_{20} = 0.7918$ g/ml) and 24.7 mN/m for 1B ($\rho_{20} = 0.7726$ g/ml). The corresponding σ/ρ values are 36.3 for the 0.1% system, 33.1 for 1A and 32.0 for 1B. Pronounced surface tension effects causing errors in viscometry seem, therefore, unlikely and no corrections for surface tension effects were introduced below in the calculation of the viscosities.

Viscometry

There is a steep increase of the viscosity near 10 wt% tyloxapol as illustrated in the viscosity-concentration curve (Fig. 5). This confirms the existence of significant particle interactions in this concentration range as already observed in the X-ray scattering patterns. The density of the micellar solutions increases linearly with concentration.

The viscosity of systems containing less than about 1.4 wt% increases linearly with concentration. The intrinsic viscosity $[\eta]$ of dilute colloidal solutions is given by:

$$\frac{(\eta_{rel} - 1)}{c} = [\eta] + D \cdot c$$

where $\eta_{rel} = \eta/\eta_0$ and η is the viscosity of the solution of concentration c (in g/dl) and η_0 that of the solvent. D is a constant which depends on the interactions in the system which give rise to perturbing hydrodynamic effects. For impenetrable spheres of density ρ the value of $[\eta]$ is $0.025/\rho$ (dl/g). Deviations are usually interpretable as resulting from particle anisotropy or solvation.

For detergents c must refer to the concentration of micelles rather than to the total detergent in solution (Kushner and Hubbard, 1954). Consequently, η_{rel} is the viscosity of the micelle solu-

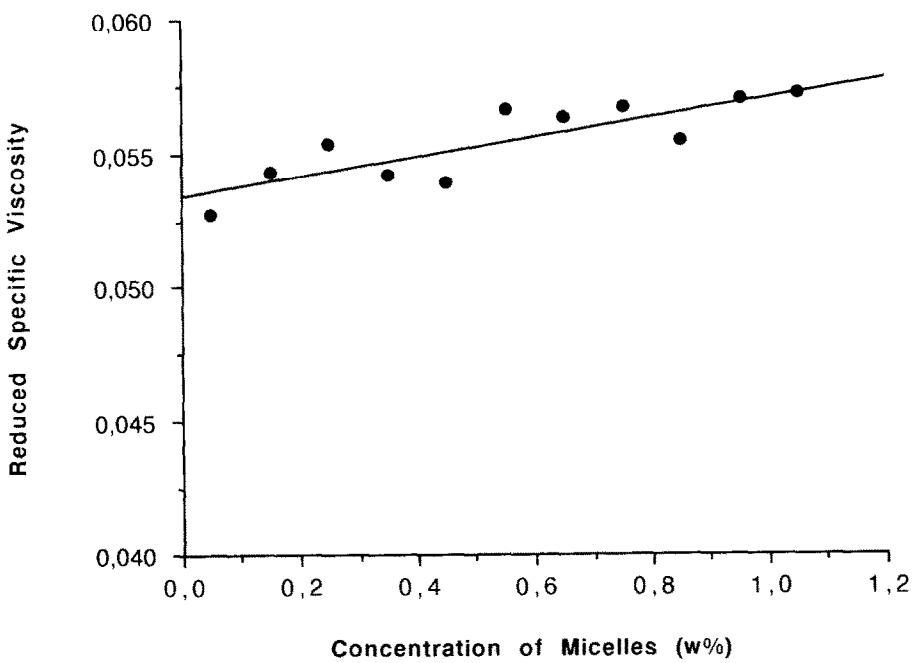

Fig. 6. Reduced viscosity as a function of concentration of detergent assuming a critical micelle concentration of 0.25% (w/v).

tion relative to that of some arbitrary concentration of detergent, the monomer saturation concentration c_s, above which it can be safely assumed that essentially all added detergent is incorporated into micelles (Kushner et al., 1952). The concentration of micelle-forming detergent c_m is then given by $c_m = c - c_s$. Kushner and Hubbard (1954) have described the difficulties in the determination of the monomer saturation concentration of the nonionic detergent Triton X-100, a condensate of ethylene oxide with *p*-(1,1,3,3-tetramethylbutyl)phenol, which can be considered as the repeating unit of tyloxapol.

Assuming tyloxapol monomer saturation concentrations below 0.2% (g/ml) results in a marked deviation from linearity of the reduced specific viscosity versus micellar concentration curve at low concentrations. Almost linear plots (Fig. 6) are obtained for a critical micellar concentration (CMC) value of 0.25% (w/v) which is close to that (0.3%) found by Kushner and Hubbard (1954) for Triton X-100. The intrinsic viscosity $[\eta]$ of tyloxapol is then 0.053 dl/g.

The density of tyloxapol is 1.0963 g/ml at 20°C but that of the micelles is expected to be close to unity as found for hydrated polyoxyethylene chains (Adam et al., 1984).

The expected value of the intrinsic viscosity would thus be close to 0.025 dl/g since at low concentrations (3 wt%) the systems contain spherical micelles with a diameter around 7 nm.

The large intrinsic viscosity of the solutions is likely to be due to hydration of the polyoxyethylene chains resulting in considerable swelling of the micelles. The volume of the hydrated micelles is about 2.2 times larger than the theoretical dry volume. Assuming an average molecular weight of 660 for the average repeating unit of tyloxapol (i.e., one molecule of Triton X-100 plus one $-CH_2-$ group), the average number of water molecules attached to each single polyoxyethylene chain of the micelles is estimated to be around 44. This value is comparable to that reported for Triton X-100 micelles (Kushner and Hubbard, 1954). Each tyloxapol repeating unit is expected to contain 10 oxygen atoms corresponding to 10 ethylene oxide units plus one additional phenolic oxygen. Thus, on average 4 mol of water interact with each mol of ethylene oxide possibly forming polytetrahydrates.

The ionic strength of the aqueous phase has no significant influence on the intrinsic viscosity of the tyloxapol micelles. The intrinsic viscosity of the micelles in 0.04 and 0.14 M NaCl solutions is 0.052 dl/g assuming a CMC value of 0.275% (w/v).

Discussion

X-ray scattering indicates the existence of a liquid crystalline hexagonal phase between 37.5 and 65 wt% tyloxapol, however, the data do not one allow to distinguish between hexagonal phases consisting of cylindrical aggregates filled with amphiphile and surrounding water, and reversed hexagonal phases consisting of polar cylinders in a non-polar lipophilic environment. The position of the hexagonal phase in the concentration/temperature phase diagram and its ability to solubilize the hydrophilic dye methylene blue but not the lipophilic dye Sudan Red 7B (Westesen, 1994) suggests, however, that the hexagonal phase belongs to the first group (middle phase or M_1 phase). Whereas the hexagonal lattice parameter a could be derived, the radius r of the rod-shaped aggregates, which can be obtained from Eqn 3:

$$r = \left[2 \cdot \phi / (\Pi \cdot \sqrt{3})\right]^{1/2} \cdot d$$

where ϕ is the volume fraction of the amphiphile, could not be calculated as usually done for ionic detergents. In the latter case, the hydrophobic part of the molecule is huge compared to its hydrophilic moiety. For non-ionic detergents the situation is reversed. In the case of tyloxapol where not only the terminal ethylene oxide units must be highly hydrated the value of ϕ that must be taken into account is that of the hydrated amphiphile which, unfortunately, could not reliably be measured or estimated. Assuming close contact between cylindrical micelles in the hexag-

onal phase a value of ϕ close to 0.9 is found in all cases with micellar diameters of 7.0 nm at 37.5 wt%, 6.2 nm at 50 wt% and 5.7 nm at 65 wt%.

The X-ray data indicate that the molten hexagonal compositions with high water content ($\geq$ 57.5%) transfer on cooling into hexagonal structures with lattice parameters deviating significantly from those of the equilibrated systems before melting. Polarized light microscopy indicates that these hexagonal systems with high water content do not retransform into their equilibrium state directly but form intermediate two-phase systems consisting of an optically isotropic (aqueous) phase and a hexagonal phase.

The cubic nature of the narrow phase around 70 wt% tyloxapol was derived from the spacing ratios of reflections which differ clearly from that of the common lyotropic liquid crystalline lamellar and hexagonal phases. Its three-dimensional structure could not be unequivocally assigned from the eight reflections in the X-ray pattern. The narrow concentration and temperature range of the cubic phase compared to the others suggests that highly specific conditions are required for its formation. These constraints also explain its extremely slow formation from its melt on storage at room temperature.

As with the hexagonal phases, the maximum d values of the lyotropic liquid crystalline lamellar phase (neat or G phase) decrease with decreasing water content of the systems. The low intensity of the reflections after filling this phase into the sample holder is indicative of weak supramolecular interactions which are significantly affected by the shear forces during this procedure.

Tyloxapol may be considered as a formaldehyde polymer of a polyoxyethylene condensate of *p*-(1,1,3,3-tetramethylbutyl)phenol, e.g., a formaldehyde polymer of Triton X-100. The polar and apolar regions of the tyloxapol molecule are perpendicular to the polyphenol chain. It thus seems likely that the lyotropic liquid crystalline phases of tyloxapol exhibit orientations and arrangements of tyloxapol molecules similar to those expected for its repeating unit. The length of extended Triton X-100 has been estimated from bond lengths and bond angles to be approx. 4.6 nm (Kushner and Hubbard, 1954). About 25% of the length corresponds to the hydrophobic *p*-(1,1,3,3-tetramethylbutyl)phenol and about 75% to the polyoxyethylene chain. The X-ray data of tyloxapol can qualitatively be interpreted on this basis if one also neglects its molecular weight distribution.

The spherical micelles at 3% have a diameter around 7 nm and contain an estimate of 44 bound water molecules per polyoxyethylene chain. The upper limit of the diameter of the rods of the hexagonal systems is given by the lattice parameter a, e.g., about 5.7–7 nm depending on the water concentration of the hexagonal system. Taking an average molecular weight of 660 for the repeating unit of tyloxapol the number ratio of water molecules per polyoxyethylene chain can be estimated to be 20 for the 65 wt% hexagonal system and 60 for the 37.5 wt% system. The most temperature resistant hexagonal systems with a tyloxapol concentration between 47.5 and 50 wt% have a water/polyoxyethylene chain ratio of 41–37 indicating that polytetrahydrates represent the most stable hexagonal composition. Polytetrahydrates also appear to be the most stable lyotropic hexagonal phases of Triton X-114 (Heusch, 1984). It seems most likely that in both cases the dimensions of the structural units are the result of the interaction of antiparallel molecules. The significant deviation of the diameters of micelles and rods from double the length of one fully extended repeating unit of about 9 nm probably results from the hydration of the polyoxyethylene chains. The estimated length of Triton X-100 is based on the zigzag configuration for the polyoxyethylene chain. Other configurations have been described such as the meander chain and the helical chain (Rösch, 1967) which result in a significant contraction of the polyoxyethylene chain. The length of the oxyethylene units in the zigzag chain amounts to about 3.4 Å, but in the meander chain to about 2 Å (Rösch, 1967). An overlap of the hydrophobic parts of antiparallel repeating units could not result in the required deviation of about 2 nm and seems unlikely due to the bulkiness of the branched octyl moieties.

The upper limit of the thickness of the lamellar layers is determined by the repeat distance, e.g., about 4.8 nm. Marsden and McBain (1948)

found for frozen Triton X-100, which is liquid at room temperature, a repeat distance of 4.65 nm. The values found for the lamellar layers of the liquid crystalline tyloxapol/water systems as well as for the frozen, e.g., crystalline, Triton X-100 are, however, similar to the length of one fully extended repeating unit, e.g., 4.6 nm. It is unlikely that the lamellar layers consist of single molecules. Based on X-ray data a crystal lattice arrangement for polyoxyethylene *p,t*-octylphenols was therefore proposed which consists of oppositely oriented molecules interlocked via their polyoxyethylene chains and their *t*-octylphenol portions (Rösch, 1967). Although the repeat distance of the liquid crystalline lamellar systems of tyloxapol would be consistent with such a model, the required interlocking of molecules seems incompatible with the low viscosities of the liquid crystalline lamellar systems which indicate the occurrence of shear planes between the lamellae. Moreover, tyloxapol contains the much bulkier *p*-(1,1,3,3-tetramethylbutyl)phenol chains which probably prevent the interlocking of the hydrophobic chains. The crystal lattice model thus seems inappropriate to describe the liquid crystalline arrangements despite the similarity in the X-ray data. All lamellar systems appear to be at least two-phase systems in the polarized light microscope. The water content of the liquid crystalline lamellar phase cannot be estimated as long as the nature of the dispersed isotropic phase is not unambiguously established.

While all techniques demonstrate the existence of a hexagonal and a cubic one-phase region in the phase diagram, polarizing microscopy was the only one indicating the coexistence of a lamellar liquid crystalline phase and a dispersed isotropic phase as well as the occurrence of crystalline material in all systems containing more than 75 wt% tyloxapol. Sedimentation of the crystalline material has been observed on storage and may be the reason for the lack of sharp reflections in the X-ray patterns of mixtures with tyloxapol concentrations above 75 wt%.

The lyotropic liquid crystalline one-phase regions in the phase diagram are separated from each other by narrow two-phase regions. A narrow two-phase region was also observed between the micellar and the hexagonal phase (see Fig. 6 in Westesen (1994)).

The two parts of this study illustrate that a consistent picture can be obtained by combining complementary methods. Ideally, of course, one would need to make the optical and X-ray observations simultaneously using a very narrow X-ray beam to record the patterns of the different phases in the two-phase systems.

Conclusions

Despite its high molecular weight, tyloxapol behaves like a typical low-molecular weight amphiphile. At room temperature with increasing water concentration mixtures of tyloxapol and water form lamellar, cubic and hexagonal liquid crystalline phases but at body temperature only the hexagonal phase is left.

The complexity of lyotropic liquid crystalline phases and their temperature dependent phase boundaries are of special interest for the drug and pharmaceutical additive properties of tyloxapol. The vicinity of the extended micellar region and the hexagonal phase and the lack of headgroup charges may explain its ability to form fairly stable oil-in-water emulsions with average particle diameters below 100 nm (Westesen, unpublished data). Moreover, the occurrence of various lyotropic liquid crystalline phases in aqueous mixtures and the nonionic nature of tyloxapol should allow the development of new administration systems for drugs or liquid crystalline drug carriers. The phase transition of the cubic systems below body temperature is especially interesting for the development of stiff storage forms. These would, however, easily release the drug or dispersed particles at body temperature as a result of the decrease in viscosity and the disappearance of the yield value. Conversely, the vicinity of the extended hexagonal phase region and its temperature resistance should allow the immediate in vivo formation of stiff hexagonal phases at body temperature after contact of the viscous tyloxapol with physiological liquids, e.g., in the duodenum. An investigation of these aspects as

well as a more detailed analysis of the properties of tyloxapol are in progress.

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