Synthesis and Properties of Cationic Surfactants Containing a Disulfide Bond

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Two new cationic surfactants containing a disulfide bond were synthesized, and the physical chemical characteristics and the fundamental surface-active properties were determined. These new surfactants have potential applications in the textile and cosmetic field. These compounds have been prepared by condensation of a commercial N^{α}-lauryl-N^{α},N^{α}-dimethyl amino betaine with cystine dimethyl ester or cystamine by means of the mixed anhydride method. The study of their properties revealed that these molecules are soluble in water (stable at pH ⩽ 8) and show surface activity with similar low critical micelle concentration values. Microscopic examination of water/surfactant systems containing these compounds shows that they form liquid crystals with patterns corresponding to typical hexagonal and lamellar structures.

KEY WORDS: *Bis*(quaternary ammonium halide) surfactants, cationic surfactant, cystamine amphiphile derivatives, cystine amphiphile derivatives, synthesis of surfactants.

The synthesis of amphiphilic molecules specifically designed for certain technological applications is increasing in importance. For example, to obtain a permanent effect on keratine fibers, the synthesis and application of three types of materials have been studied—reactive dyes (1), keratin polypeptide hydrolizates (2) and surfactants containing potentially reactive groups (3). In this paper we describe the synthesis, the physicochemical characteristics and the fundamental surface-active properties of two new cationic surfactants, derived from cystine and cystamine, whose molecular structures are indicated in Figure 1.

Because of the symmetrical structure of $N^{\alpha}N^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystine dimethyl ester dihydrochloride (LABC) and $N^{\alpha}N^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystamine dihydrochloride (LABK) (Fig. 1), these compounds can be considered as *bis*(quaternary ammonium halide) surfactants, recently reported (4,5) with two single saturated long-chain alkyl groups as the hydrophobic components and two quaternary ammonium salts linked through a disulfide spacer group such as $-CH_2$-CO-NH-CHR-CH_2-S-S-CH_2CHR-NH-CO-CH_2- as the hydrophilic part. The disulfide bond constitutes a potentially reactive group capable of reacting with thiol groups of reduced kerstin fibers by a thiol/disulfide interchange reaction (6,7), with the monomeric cationic thiol surfactant becoming covalently bonded to the fiber through an unsymmetrical disulfide bond. There are no reports in the literature concerning this kind of cationic surfactant, although other long-chain N^{α},$N^{\alpha'}$-diacyl amphiphilic derivatives from cystine and cystamine have been studied (8). All of these are water-insoluble compounds with cosmetic and pharmaceutical applications. The hydrophilic part of LABC and LABK differs considerably from the structures of these N^{α},$N^{\alpha'}$-diacyl cystine or cystamine amphiphile derivatives because of the presence of the quaternary ammonium groups, which are the structural factors

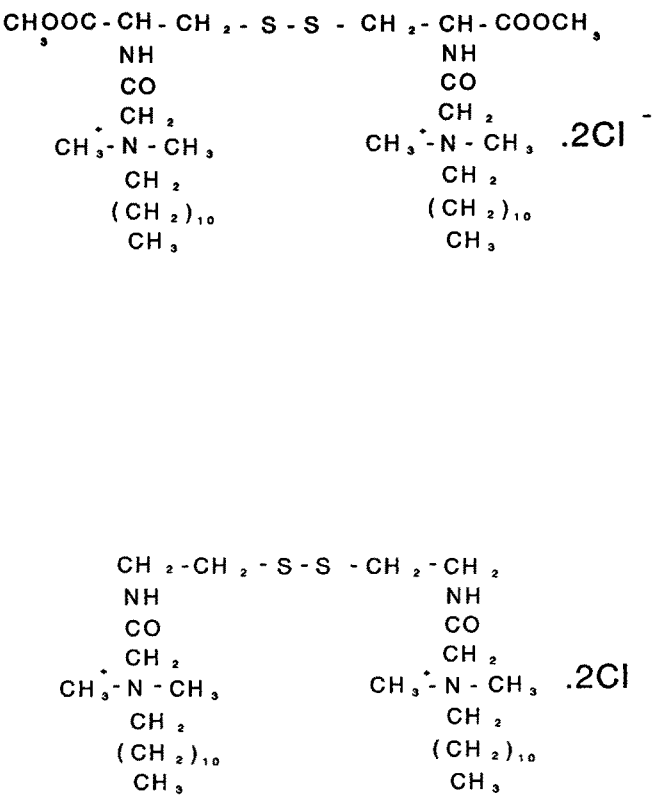

FIG. 1. Chemical structure of surfactants from $N^{\alpha}N^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystamine dihydrochloride (LABK, bottom) and $N^{\alpha}N^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystine dimethyl ester dihydrochloride (LABC, top).

responsible for their water solubility and their fiber substantivity. These two properties are essential for our further specific technological applications in the field of keratinic fibers.

The main goals of this study were: i) to prepare pure LABC and LABK compounds; ii) to determine their physicochemical characteristics; and iii) to compare their surfactant behavior in water solution on the basis of surface tension, critical micellar concentration, area per molecule at air/water interface and qualitative phase behavior. The chemical stability of both compounds also has been checked.

EXPERIMENTAL PROCEDURES

Materials. L-Cystine dimethyl ester dihydrochloride and cystamine dihydrochloride were purchased from Fluka (synthetic grade; Buchs, Switzerland). N-Lauryl N,N-dimethyl amino betaine (LAB) was prepared by Tenneco España S.A. (Div. Marchon Surfac, Barcelona, Spain). It was purified by extraction with anhydrous ethanol and recrystallized from a mixture of HCl/ethanol/ether. The purity of this material was checked by thin-layer chromatography (TLC), the two-phase mixed indicator method for zwitterionic surfactants (9), elemental analysis and

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^{1}H-NMR (nuclear magnetic resonance) analysis. Isobutyl chloroformate (IBCF) was purchased from Fluka. N,N-Dimethyl formamide (DMF) was dried over 4Å molecular sieves for 8 h. A stream of nitrogen was bubbled for three hours through the DMF prior to use.

TLC was performed on Merck (Darmstadt, Germany) Silica Gel 60 plates and used in the whole process of synthesis to monitor the course of the reaction and the homogeneity of substances. The solvent systems were: A, butanol/pyridine/acetic acid/water (60:20:6:24); B, chloroform/methanol/acetic acid/water (60:25:2:4); and C, ethyl acetate/methanol (50:50). Primary amino groups were detected by TLC with ninhydrin spray (10), disulfide functions with nitroprusiate after reduction to sulfhydryl groups (11), and quaternary ammonium group was detected with Dragendorff spray (12). The purity of the final products was checked by elemental analysis, ^{1}H-NMR and the two-phase indicator method for cationic surfactants (13). Optical rotations were measured on a 141 Perkin-Elmer Spectropolarimeter (Norwalk, CT). Proton Magnetic Resonance (H-NMR) spectra were measured on a Bruker WP 805 Spectrometer (Karlsruhe, Germany).

Preparation of LABC. IBCF (3.57 mmols) was added to a solution of LAB (3.57 mmols) and *N*-methylmorpholine (3.57 mmols) in DMF (25 mL) at a low temperature (−15°C). After 2 min a chilled solution of L-cystine dimethyl ester dihydrochloride (1.78 mmols) and *N*-methylmorpholine (3.57 mmols) in DMF-H_2O (11.5 mL, 22:1 by vol) was added to the reaction mixture. The solution was stirred for 1 h at 0°C, left overnight at room temperature and evaporated under vacuum. The resulting crude product was washed with diethyl ether to eliminate the urethane by-product. Afterwards it was dissolved in $CHCl_3$ and washed successively with 10% citric acid solution and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness under vacuum. The residue was subjected to preparative column chromatography (3.0 × 50 cm) on Silica Gel 60 (40–60 μm), eluting with $CHCl_3$/MeOH/AcOH/H_2O (60:25:2:4, by vol). The fractions containing the pure product were evaporated, and the product was repeatedly lyophilized from H_2O, yielding a hygroscopic white material.

Preparation of LABK. IBCF (3.57 mmols) was added to a solution of LAB (3.57 mmols) and *N*-methylmorpholine (3.57 mmols) in DMF (25 mL) at a low temperature (−15°C). After 2 min a chilled solution of cystamine dihydrochloride (1.78 mmols) and *N*-methylmorpholine (3.57 mmols) in DMF-H_2O (11.5 mL, 22:1 by vol) was added to the reaction mixture. The solution was stirred for 1 h at 0°C, left overnight at room temperature and evaporated under vacuum. The resulting crude product was dissolved again in 10 mL of DMF, cooled at −15°C and added to a solution containing IBCF (1.78 mmols), LAB (1.78 mmols) and *N*-methylmorpholine (1.78 mmols) in DMF (25 mL). The new reaction mixture was stirred for 1 h at 0°C, left overnight at room temperature and evaporated under vacuum. The purification of the residue was carried out in the same manner as the LABC. Yields, physical characteristics and spectroscopic features of LABC and LABK are given in Table 1.

Method for surface tension. A DuNoüy tensiometer (Lauda, Königshofen, Germany) with a platinum ring was used for surface tension measurements (γ). Water/surfactant solutions of different concentrations were prepared and allowed to equilibrate at 25°C between 15 and 30 min.

Methods for critical micellar concentration (CMC), saturation absorption (Γ) and area per molecule (A_m). CMC of LABC and LABK were determined from the surface tension/concentration curves. The saturation adsorption values at the air/water interface and the A_m were calculated with the Gibbs adsorption equation (14).

Method for qualitative phase behavior. Qualitative phase behavior of binary water/LABC and water/LABK systems as a function of temperature was carried out by optical microscopy. Optical examinations were performed according to the "flooding" or "penetration" method of Lawrence (15,16) by means of a polarizing microscope equipped with a hot stage. In a "flooding" experiment, water is allowed to diffuse into an anhydrous surfactant placed between a slide and a cover-slip. After a short time, gradients in composition are produced, and the different mesophases develop as separate rings around crystalline surfactant.

Chemical stability. Chemical stability was determined as a function of the pH and temperature in molar aqueous solutions containing LABC and LABK. The solutions

TABLE 1

Physical Characteristics and Spectroscopic Features of LABC and LABK[a]

Compound	Yield (%)[b]	$(\alpha)_D^{22}$	Elemental analysis (cal.%)	Elemental analysis (found %)	IR(KBr):ν,cm^{-1} NH	CO	CNH	^{1}H-NMR: δ (solvent $CDCl_3$)	Rf
LABC	60	−28.8	C 55.50 H 9.26 N 6.48 S 7.40	C 55.01 H 9.66 N 5.51 S 6.19	3400	1750 1690 1580	1220	0.88[3H,*t*,CH_3-$(CH_2)_{10}$-] 1.2-1.8[14H,*m*,CH_3-$(CH_2)_{10}$-CH_2-N-] 3.4[6H,*s*,-CH_2-N(CH_2)$_2$-CH_2)-] 3.1[2H,*d*,-S-CH_2-CH-] 3.7[3H,*s*,-O-CH_3] 4.8[1H,*s*,S-CH_2-CH-NH-CO]	0.46 (A) 0.49 (B) 0.61 (C)
LABK	40	0	C 54.44 H 10.45 N 7.05 S 8.07	C 54.79 H 10.59 N 6.20 S 7.82	3400	1680 1560	1270	0.9[3H,*t*,CH_3-$(CH_2)_{10}$-] 1.2-1.8[14H,*m*,CH_3-$(CH_2)_{10}$-CH_2-N-] 3.3[6H,*s*,-CH_2-N(CH_2)$_2$-CH_2] 3.1[2H,*m*,-CO-NH-CH_2-CH_2-S-] 3.4[2H,*m*,CO-NH-CH_2-CH_2-S] 3.5[2H,*m*,N(CH_3)$_2$-CH_2-CO]	0.43 (A) 0.50 (B) 0.40 (C)

[a]LABC N$^\alpha$N$^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystine dimethyl ester dihydrochloride derivative; LABK, N$^\alpha$N$^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystamine dihydrochloride derivative; IR, infrared; NMR nuclear magnetic resonance.
[b]Before column chromatography.

were adjusted to pH 5.0, 6.0, 7.0, 8.0 and 9.0 and maintained at 25 and 50°C for 24 h. The stability of the compounds was controlled by checking the homogeneity of solutions with TLC.

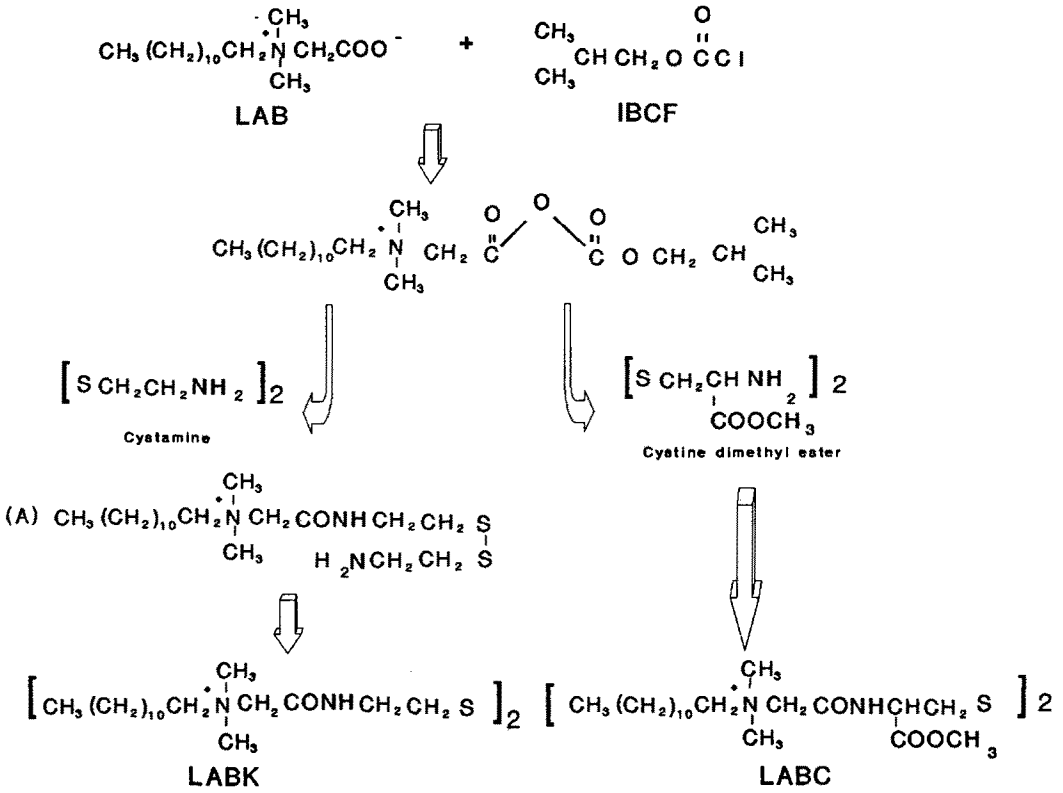
RESULTS AND DISCUSSION

The methods applied for the synthesis of the *bis*(quaternary ammonium) amphiphilic derivatives of cystine (LABC) and cystamine (LABK) are summarized in Scheme 1. LABC and LABK were obtained by the well-known mixed anhydride method that utilized the following reactions: i) conversion of N-lauryl N,N-dimethyl amino betaine to the mixed anhydride intermediate by means of IBCF as reagent; and ii) aminolysis of the mixed anhydride intermediate by the amino groups of cystine dimethyl ester or cystamine to yield the compounds LABC and LABK, respectively.

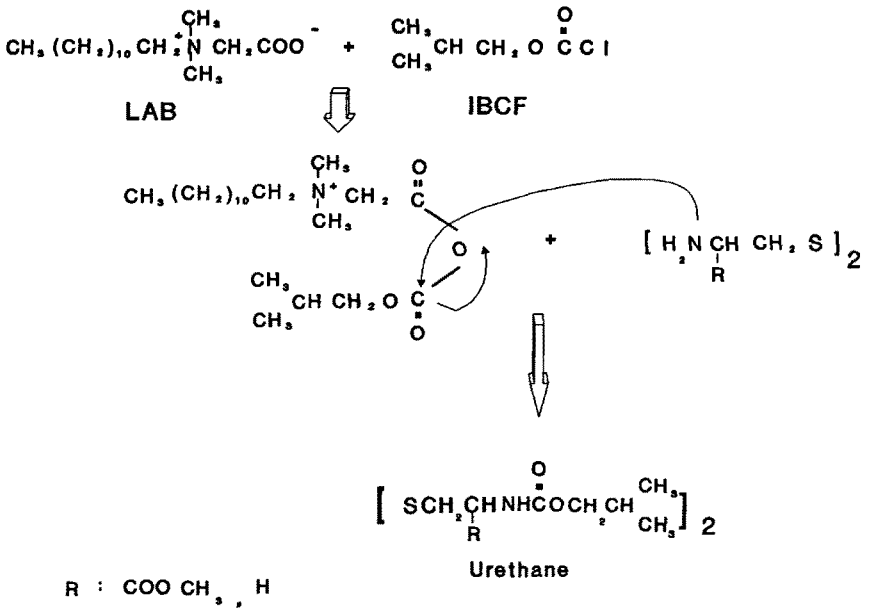
The reaction was carried out in a liquid phase DMF/H_2O with *N*-methyl morpholine as the tertiary base. These conditions have been described recently to prepare other cystine and cystamine derivatives (17). In this medium only 10% of urethane was formed, which was easily eliminated by ethyl ether extractions. Urethane is the main undesired by-product in the mixed anhydride method and is produced by the attack of the nucleofile on the carbonic acid carbonyl (18) (see Scheme 2).

LABC was obtained in the one-step condensation with a 60% yield and was purified by column chromatography, yielding a hygroscopic white material that was homogeneous by TLC. This product migrated on TLC at Rf values different from those of the starting materials. The presence of the quaternary ammonium group was verified by a positive Dragendorff reaction (orange color). The formation of the amide linkage was verified by a negative ninhydrin reaction and a positive Cl_2/O-tolidine reaction. The presence of the disulfide bond was concluded from the positive reaction with sodium nitroprusiate after treatment with a cyanide solution. LABK was obtained in a two-step condensation with a 40% yield. The first-step condensation yielded an incomplete reaction (monoacylation of one amino group of cystamine), which resulted in the formation of product A (Scheme 1) with a 50% yield. Complete acylation of cystamine was carried out (90%) by the addition of a second portion of the mixed anhydride to the monoacylated derivative of cystamine. Yields and analytical data of LABC and LABK are given in Table 1. Infrared (IR), ^{1}H-NMR and elemental analysis were consistent with the expected structures.

Aqueous solutions of 1 mM LABC and LABK were titrated by the two-phase method (13) and showed a purity of 98%. Both compounds LABC and LABK were whitish hygroscopic solids. LABC was optically active, whereas LABK was inactive because of the absence of an asymmetric carbon atom. The solubility at room temperature of both compounds was partially checked, and the results showed that they were soluble in water, alcohol and chloroform, but insoluble in ethyl ether. Chemical stability for LABC and LABK was qualitatively tested in an aqueous solution as a function of the pH and temperature. The TLC parameters of the tested solution revealed that: i) both compounds were decomposed at pH > 8.0 at room temperature, probably due to a destruction of the disulfide bridge; ii) the solutions were homogeneous and therefore stable at pH ⩽ 8.0 even at



SCHEME 1



SCHEME 2

TABLE 2

Surface properties of the Synthesized Compounds

Compound	Surface Tension at the CMC (mN/m)	CMC (mols/1 × 10^{-3})	Area per molecule ($Å^2$)
LABC	35	0.021	102
LABK	31	0.041	119

[a]Abbreviations as in Table 1. CMC, critical micelle concentration.

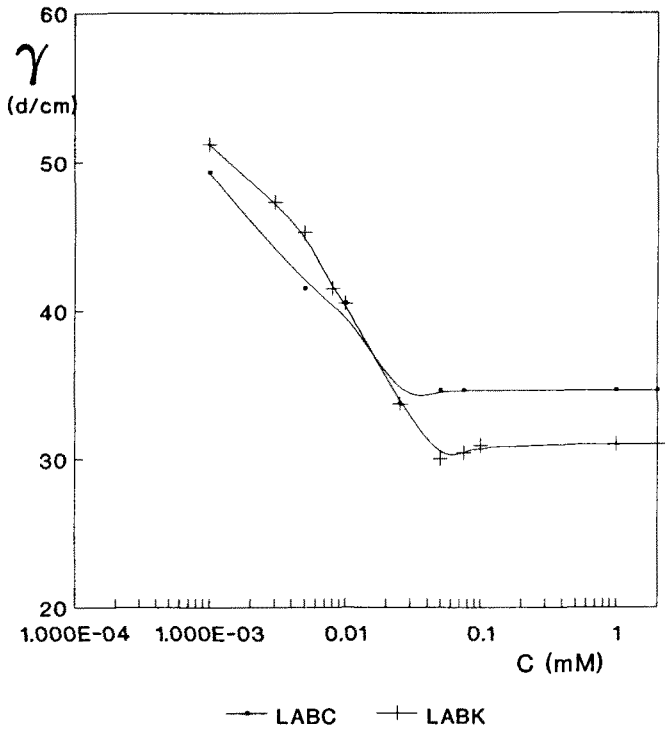


FIG. 2. Surface tension against log-concentration at room temperature.

50°C, giving spots whose Rf values were the same as those of the reference. Both compounds, LABC and LABK, presented a surfactant-like behavior by producing copious foam in an aqueous solution.

To assess the surface-active properties of both compounds, the following parameters were determined from the surface tension-log concentration plots (Fig. 2): CMC values, surface tension at the CMC values, and A_m. These results are shown in Table 2. As can be observed from the results, the surfactant properties of LABC and LABK are similar owing to their structural analogy. Both compounds have low CMC values in comparison with other series of *bis*(quaternary ammonium) surfactants with an alkane chain as a spacer group. Zana and coworkers (4), in their studies on alkanediyl α-ω*bis*(dimethyl alkyl ammonium bromide) surfactants, C_sH_{2s}-$\alpha\omega$[$(CH_3)_2$ N^+ $C_mH_{2m+1}Br^-]_2$ reported CMC values of 1.0 mM for the compound with s = 6 and m = 12, and 0.3 mM for s = 12 and m = 12. It is likely that the long length and specific structural characteristic of the spacer group in LABC and LABK exerts an important influence on the structural conformation of the surfactant, thus producing changes in the CMC values.

The A_m data for both compounds are in agreement with those found for other *bis*(quaternary ammonium) surfactants (90–119 × 10^{-20} m^2) (19). To know the number and type of liquid crystalline structures formed in the water/LABC and water/LABK systems, optical microscopy examinations were performed according to the

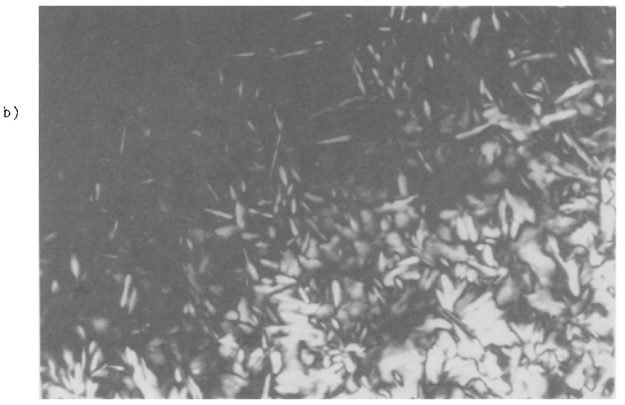


FIG. 3. Liquid crystalline structures formed in the water/$N^{\alpha}N^{\alpha'}$*bis*(N-lauryl N,N dimethyl glycine) cystine dimethyl ester dihydrochloride system: a, hexagonal structure; b, crystalline phase.

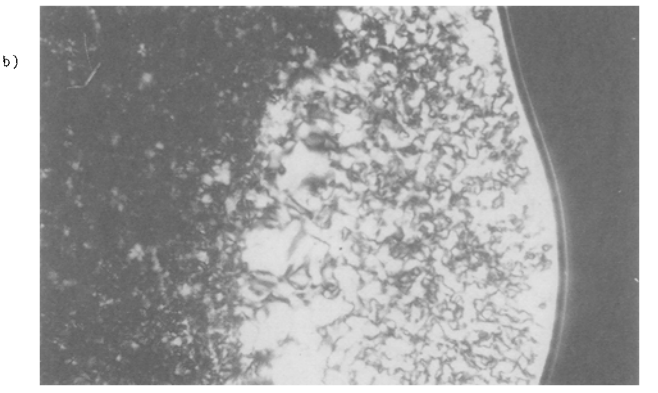


FIG. 5. Liquid crystalline structures formed in the water/$N^{\alpha}N^{\alpha'}$*bis*-N-lauryl N,N dimethyl glycine) cystamine dihydrochloride system: a, hexagonal liquid crystalline structure; b, lamellar liquid crystalline structure.

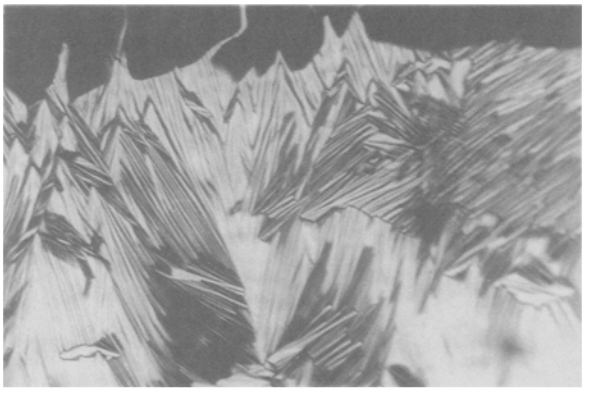


FIG. 4. Liquid crystalline structures formed in the water/$N^{\alpha}N^{\alpha'}$*bis*-(N-lauryl N,N dimethyl glycine) cystine dimethyl ester dihydrochloride system by increasing the temperature from 19°C (a) to 45°C (b).

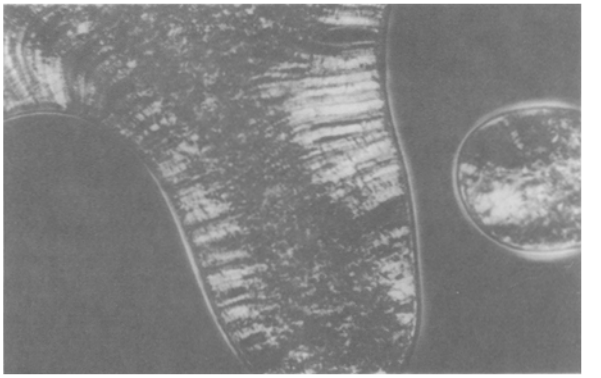


FIG. 6. Melting point of the hexagonal liquid crystalline phase (a), and the lamellar phase (b).

method described by Lawrence (15,16). For the water/LABC system only a hydrated solid surfactant was observed at temperatures below 14°C. At 14°C, two anisotropic bands were distinguished. One corresponds to a liquid crystalline phase with a characteristic hexagonal pattern (Fig. 3a), and the other to a crystalline phase (solid surfactant) (Fig. 3b). by increasing the temperature to 19°C (Fig. 4a), the hydrated solid surfactant disappeared, and only one hexagonal liquid crystalline phase showing three distinctive patterns was observed. At 45°C, this hexagonal liquid crystalline phase melted and only an isotropic liquid phase remained (Fig. 4b). A different phase behavior was observed for the binary water/LABK system. At 14°C, two different anisotropic bands were observed corresponding to two different liquid crystalline phases (Fig. 5)—the external band (Fig. 5a), which corresponds to a lower surfactant concentration, was narrow and showed a typical hexagonal liquid crystalline structure, and the internal band (Fig. 5b), corresponding to a higher

surfactant concentration, which showed a typical structure of lamellar liquid crystalline. The melting point of the hexagonal liquid crystalline phase was 16°C (Fig. 6a), and that of the lamellar phase was 31°C (Fig. 6b). At 31°C, only one liquid isotropic phase was observed. The formation of a lamellar liquid crystalline phase in this system may be attributed to the higher hydrophobic character of LABK with respect to that of LABC. Modification of the chemical and physical structure of the keratin fibers by treatments with these specific compounds to impart new desirable and permanent characteristics could constitute an interesting technology to improving the properties of fibers. Studies of the application of these surfactants in keratin fibers are currently in progress. Fundamental properties of these surfactants will be carried out in collaboration with another research group.

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