

Amphiphilic Compounds Containing a Carbamate Fragment: Synthesis, Aggregation, and Solubilizing Effect

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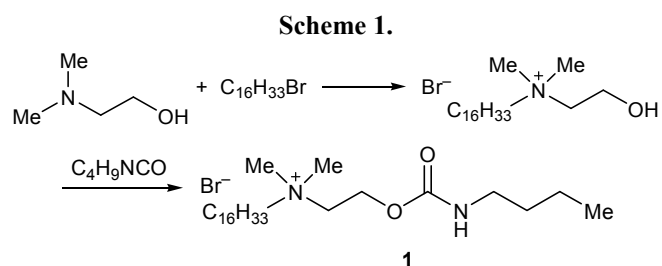
Abstract—A new cationic surfactant containing a butylcarbamate fragment as the head group and hexadecyl radical as hydrophobic component has been synthesized and characterized. Its aggregation parameters have been determined by tensiometry, conductometry, and dynamic light scattering, and its solubilizing capacity for naphthalene and anthracene has been estimated.

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Search for and design of new amphiphilic compounds conform to the modern trends in the development of organic and bioorganic chemistry. Amphiphilic molecules are widely used as building blocks for the construction of nanosized supramolecular systems capable of reducing interface surface tension, exerting high solubilizing effect, and affecting the stability and functional properties of the solubilize [1–3]. New amphiphiles should meet a number of requirements to ensure their possible application in biotechnologies, pharmacology, and medicine. These include high efficiency under mild conditions at a low concentration, low toxicity, and the ability to overcome biological barriers. Over the past decade, amphiphilic compounds belonging to new classes, primarily cationic surfactants have been synthesized and characterized. Among them, dicationic surfactants with a low aggregation threshold, surfactants capable of degrading under certain conditions, and surfactants containing fragments of natural compounds (to improve their biocompatibility) may be noted [4–9]. A specific feature of surfactants containing a carbamate fragment is their ability to undergo hydrolytic decomposition under physiological conditions. Such carriers conform to the biodegradability criterion, and they can release active molecules after overcoming biological barriers, including the blood–brain barrier, which advantageously distinguishes them from other cationic surfactants

[10, 11]. However, available information on such amphiphilic compounds is very scanty.

In this article we report the synthesis and characterization of a new cationic surfactant containing a butylcarbamate fragment as the head group and hexadecyl radical as hydrophobic component, *N*-{2-[(butylcarbamoyl)oxy]ethyl}-*N,N*-dimethylhexadecan ammonium bromide (**1**). It was obtained by reaction of dimethyl(2-hydroxyethyl)hexadecylammonium bromide with butyl isocyanate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst (Scheme 1).



The aggregation behavior of surfactant **1** in aqueous solution was studied by tensiometry, conductometry, and dynamic light scattering. Figure 1 shows concentration dependences of the surface tension and specific electrical conductivity of aqueous solutions of compound **1**. The points at which the slope of the dependence changes correspond to the critical micelle con-

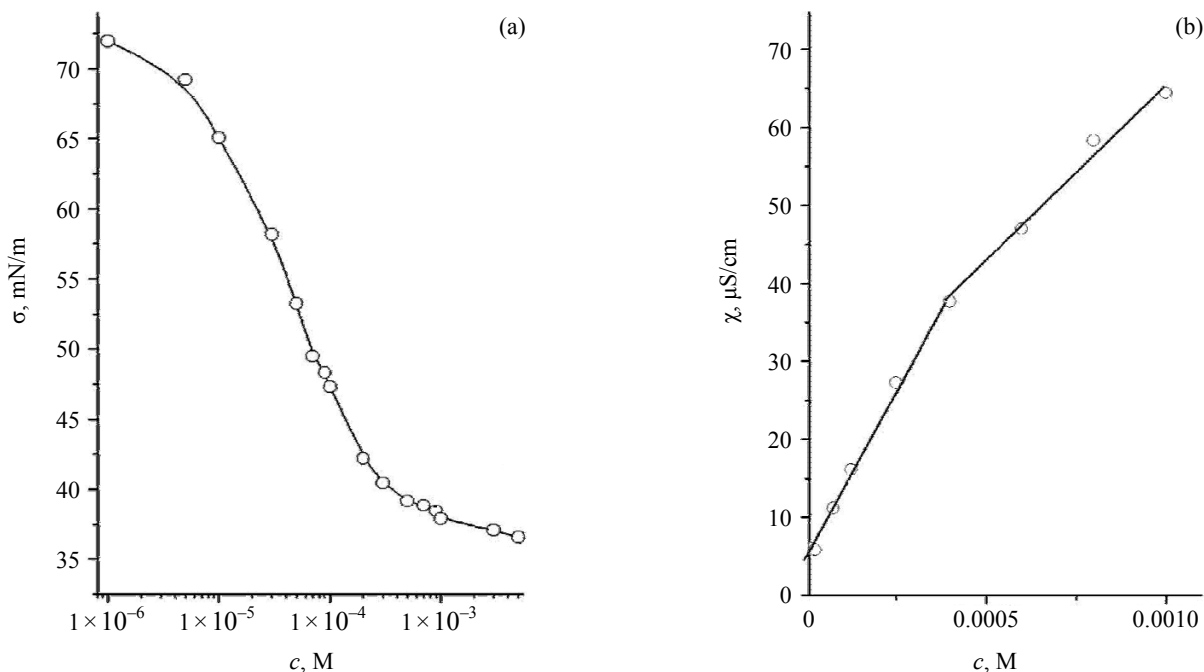


Fig. 1. Concentration dependences of (a) surface tension and (b) specific electrical conductivity of surfactant **1** in water at 25°C.

centration (CMC). The CMC values determined by different methods (Table 1) are very consistent with each other, and they indicate that micelles in solutions of **1** are formed at a concentration 4 times lower than for cetyl(trimethyl)ammonium bromide which is commonly used as reference surfactant in studies on micelle systems. The degree of counterion binding determined from the conductometric dependence as the ratio of the slopes above and below CMC is $\alpha = 0.49$, which also differentiates compound **1** from cetyl(trimethyl)ammonium bromide.

According to the dynamic light scattering data, aggregates with a hydrodynamic diameter of 2–8 nm dominate in aqueous solutions of **1** with concentrations higher than CMC (Fig. 2); these values correspond to the size of a classical spherical micelle [14]. However, the examined systems are characterized by a high polydispersity index (0.5–0.9), which suggests the presence in solution of larger particles, e.g., dynamic ensembles consisting of several micelles.

An important useful property of amphiphilic compounds is their ability to solubilize substances that are insoluble in water. This ability underlies the application of surfactants as nanocontainers for drug delivery, detergents, pollutant traps, etc., [15–17]. The solubilizing ability of **1** was studied using representatives of polycyclic aromatic compounds, naphthalene and anthracene. Interest in the latter originates from the fact that these compounds are important petrochemical and coal-chemical products which inevitably contaminate the environment and foodstuffs and create environmental and toxicological hazards [18].

Taking into account that naphthalene and anthracene are almost insoluble in water (the highest attainable concentration in water $\sim 2 \times 10^{-4}$ and 2.5×10^{-7} M for naphthalene and anthracene, respectively), their solubilization with micelles is reflected in a sharp increase of the optical density of their saturated solutions upon addition of a surfactant to a concentration exceeding the CMC. Figure 3 shows the results of

Table 1. Critical micelle concentration, degree of counterion binding (α) and solubilizing capacity (S) of carbamate surfactant **1** and cetyl(trimethyl)ammonium bromide

Compound	Critical micelle concentration, mM		α	S	
	tensiometry	conductometry		naphthalene	anthracene
Surfactant 1	0.24	0.32	0.49	0.451	0.007
Cetyl(trimethyl)ammonium bromide	0.9 [12]		0.76 [12]	0.248 [13]	0.004 [13]

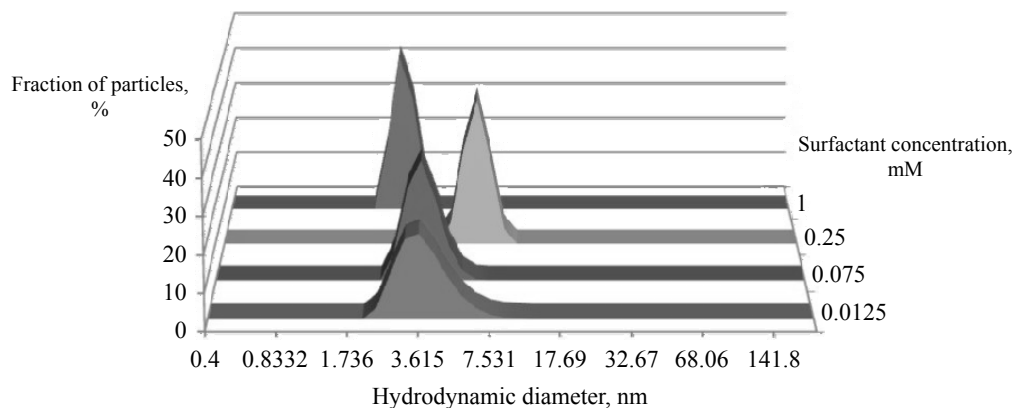


Fig. 2. Number-average size distribution of particles in micellar solutions of surfactant 1.

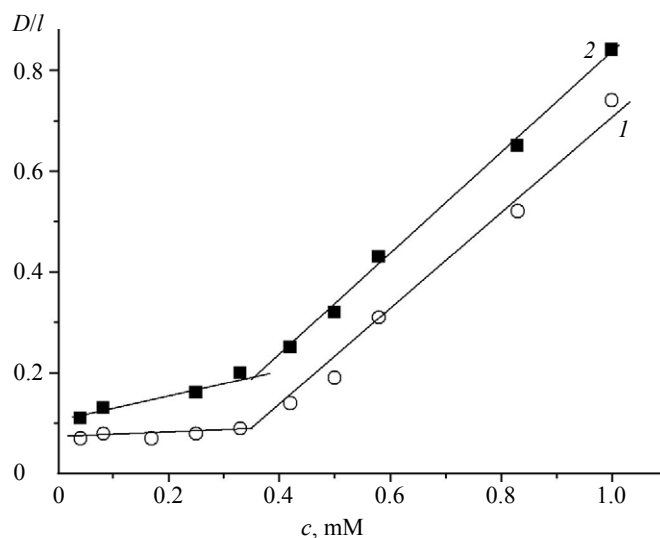


Fig. 3. Plots of the optical density at the absorption maximum of saturated solutions of (1) anthracene and (2) naphthalene versus concentration of surfactant 1.

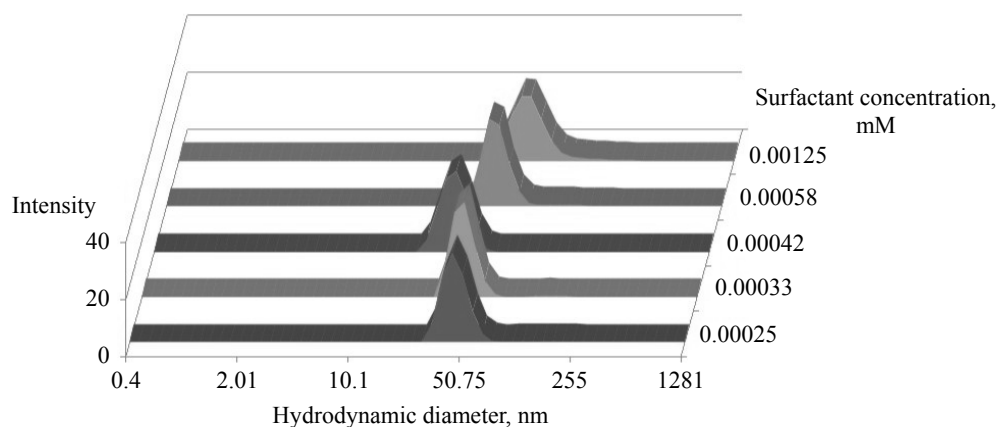


Fig. 4. Intensity-average size distribution of particles in solutions of surfactant 1 saturated with naphthalene.

spectrophotometric study of the solubility of naphthalene and anthracene in the presence of surfactant 1. These data were used to estimate the solubilizing capacity of micelles $S = b/\epsilon$, where b is the slope of the

dependence $D/l = f(c)$ and ϵ is the molar absorption coefficient; D is the optical density of a solution at the absorption maximum of the solubilize, l is the cell path length, and c is the surfactant concentration.

The optical densities were measured at λ 286 nm ($\epsilon = 2230 \text{ L mol}^{-1} \text{ cm}^{-1}$) and 255 nm ($\epsilon = 145\,000 \text{ L} \times \text{mol}^{-1} \text{ cm}^{-1}$) for naphthalene and anthracene, respectively. The results (Table 1) showed that the solubilizing capacity of carbamate surfactant **1** is almost twice as high as that of cetyl(trimethyl)ammonium bromide.

The solubilization of aromatic compounds is accompanied by considerable increase of the hydrodynamic radius of micelles of **1** (up to 50 nm). As an example, Fig. 4 shows particle size distribution in a solution of **1** with solubilized naphthalene. The distribution is monomodal and is characterized by a low polydispersity index (0.2–0.3). Presumably, the interaction of **1** with polycyclic aromatic compounds induces structural rearrangements of micelles of **1**, so that the latter partially lose their spherical shape.

In summary, the new cationic surfactant containing a carbamate fragment as the head group significantly reduces surface tension and is characterized by a high solubilizing capacity which exceeds the solubilizing capacity of traditional cationic surfactants. The low critical micelle concentration of the new surfactant makes it possible to use its smaller amount to achieve a desired effect. The procedure for the synthesis of this compound is fairly simple, and the initial compounds are accessible. All these factors could play a positive role in choosing surfactants for practical applications.

EXPERIMENTAL

The IR spectrum was recorded in KBr on a Bruker Vector-27 IR spectrometer. The ^1H NMR spectrum was recorded on a Bruker Avance spectrometer at 500 MHz using tetramethylsilane as internal standard. The mass spectra (electrospray ionization, positive ion detection) were obtained with a Bruker Amazon X instrument. The elemental composition was determined with a CHNS analyzer.

The aggregation of **1** was studied at 25°C in water purified on a Direct-Q 5 UV setup (pH 6.8–7.0, $\chi = 2\text{--}3 \mu\text{S/cm}$). The surface tension was determined by the Du Noüy ring method using a Kruss 6 tensiometer. The specific conductivity was measured with an Inolab Cond 720 conductometer. The size of aggregates formed by surfactant **1** in solution was determined with a Malvern ZetaSizer Nan dynamic light scattering photon-correlation spectrometer (He–Ne gas laser, power 10 mW, wavelength λ 633 nm, scattering angle 173°, pulse accumulation time 5–8 min); signals were analyzed with a single-plate multichannel correlator

coupled with an IBM PC using an appropriate software package for estimating effective hydrodynamic radius.

The electronic absorption spectra of solutions were measured on a Specord 250 Plus spectrophotometer using quartz cells with a 1-cm path length, which were maintained at a constant temperature. The molar absorption coefficient (ϵ) of substrates in solutions of **1** was calculated from the optical density D of a sample at the absorption maximum at a required concentration c using the formula $\epsilon = D l^{-1} c^{-1}$. The molar absorption coefficient of anthracene was determined in *n*-decane because of its very low solubility in water and aqueous surfactant solutions.

The solubilizing effect of micelles of **1** was studied by measuring the maximum concentration of naphthalene or anthracene in surfactant solution. For this purpose, a solution of **1** with a concentration of 0.05–5.0 mM was prepared, and a known amount of a substrate was added. The mixture was vigorously stirred for 2 h and was left to stand for 48 h at a constant temperature (25°C) for equilibration. The undissolved material was filtered off, and the electronic absorption spectrum of the filtrate was recorded. The substrate concentration was determined from the optical density D at the absorption maximum and molar absorption coefficient.

Dried and distilled solvents and commercially available reagents (without additional purification) were used in the synthesis of **1**: 1-bromohexadecane (98%) and 1,4-diazabicyclo[2.2.2]octane (97%) from Acros Organics; butyl isocyanate (98%) and 2-(dimethylamino)ethanol (98%) from Aldrich. Dimethyl(2-hydroxyethyl)hexadecylammonium bromide was synthesized by the reaction of 2-(dimethylamino)ethanol with 1-bromohexadecane according to the procedure described in [19, 20]. Naphthalene and anthracene with a purity of $\geq 99\%$ (Sigma–Aldrich) were used without additional purification.

***N*-{2-[(Butylcarbamoyl)oxy]ethyl}-*N,N*-dimethylhexadecan ammonium bromide (**1**)**. A mixture of 3 g (7.6 mmol) of dimethyl(2-hydroxyethyl)hexadecylammonium bromide, 2.26 g (22 mmol) of butyl isocyanate, and 0.01 g (0.09 mmol) of 1,4-diazabicyclo[2.2.2]octane in 20 mL of acetonitrile was stirred for 2 h at 55°C in a flask equipped with a reflux condenser. When the reaction was complete, volatile components were removed under reduced pressure, and the dry residue was recrystallized twice from ethyl acetate and dried under reduced pressure until constant weight. Yield 2.45 g (65%), mp 73–75°C. IR spectrum, ν ,

cm⁻¹: 3236, 2920, 2852, 1720, 1526, 1471, 1378, 1246, 1140, 1060, 969, 947, 721. ¹H NMR spectrum (CDCl₃), δ, ppm: 0.88–0.94 m (6H, CH₂CH₃), 1.27–1.37 br.m [(CH₂)₁₃CH₂CH₃, NHCH₂CH₂CH₂CH₃], 1.51–1.54 m (2H, NHCH₂CH₂CH₂CH₃), 1.75 s [2H, (CH₂)₁₃CH₂CH₃], 3.17 t (2H, CH₂O, *J* = 6.67 Hz), 3.49 s [6H, N⁺(CH₃)₂], 3.60 s (2H, NHCH₂), 3.97 s [2H, N⁺CH₂(CH₂)₁₄CH₃], 4.56 s (2H, N⁺CH₂CH₂O), 5.98 br.s (1H, NH). Mass spectrum: *m/z* 413.5 [*M* – Br]⁺. Found, %: C 60.50; H 10.14; Br 16.12; N 5.28. C₂₅H₅₃BrN₂O₂. Calculated, %: C 60.83; H 10.82; Br 16.19; N 5.67. *M* 493.6.

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