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Carbamate-bearing surfactants: Micellization, solubilization, and biological activity

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ABSTRACT

Herein novel cationic carbamate-bearing surfactants have been synthesized and characterized as effective building blocks for the development of polyfunctional nanosystems showing solubilizing, antimicrobial and membrane-tropic activity. For this purpose aggregation behavior of the surfactants has been evaluated, with the structure of head group and hydrophobicity varied. Their concentration and temperature ranges of micelle formation have been determined through tensiometry and conductometry: critical micelle concentration, Krafft point and adsorption parameters at the interface have been quantified. Solubilization of hydrophobic probes (Orange OT and pyrene) has been employed to determine aggregation numbers, evaluate solubilization capacity of micelles, and characterize micropolarity in the localization site of the probe. The value of LD_{50} of the carbamate-bearing surfactants has been determined (mice, intraperitoneal administration). It has been shown that the surfactants can be related to the class of moderately toxic compounds. Investigation of antimicrobial properties of carbamate-bearing surfactants has determined their significant antibacterial and antifungal activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, *Trichophyton mentagrophytes*, and *Candida albicans*.

1. Introduction

Amphiphilic compounds are mainstream as building blocks for the design of supramolecular systems showing high surface activity and solubilizing effect and act as effective nanocontainers and nanoreactors, which facilitate the administration of hydrophobic drugs into living and plant objects [1–4]. Possibilities of the employment of these substances in biotechnologies, pharmacology, and medicine make requirements of the properties of new amphiphiles, such as high performance under mild conditions and in the low concentration range, low toxicity, and the ability to overcome biological barriers, ability of multicharged interactions with loads on the one hand and biospecies on the other, morphological lability responsible for controlled structural behavior and binding/release behavior. Based on these criteria, new classes of amphiphilic compounds were synthesized and characterized in the past decade, with cationic surfactants received much attention. The latter is due to such properties of cationic amphiphiles as affinity to cell membranes and biopolyanions, e.g. DNA. Dicationic surfactants with low aggregation threshold [5–7]; degradable surfactants, which are capable of destruction under particular conditions [8–10]; and the surfactants containing fragments of natural compounds, which is critical to the increase in their biocompatibility [11–14], can be emphasized among them. Compounds containing urethane residue (organic carbamates) answer many of the above listed criteria, and therefore are of high practical importance. In particular, they can undergo of hydrolytic cleavage under physiological conditions [15–17]. When employed as carriers, they correspond to the criterion of biodegradability and can release active molecules after overcoming biological barriers involving blood brain barrier, which sets them apart from other cationic surfactants [18,19]. It should be noted that carbamate-bearing molecules play an important role in modern drug discovery and medicinal chemistry. Organic carbamates (or urethanes) are structural elements of many approved therapeutic agents. One example is that the simplest representative of this class of compounds, namely, ethyl carbamate, forms the basis for the drug urethane, which is used as sedative and tranquilizer, as well as anticonvulsant in children clinics. Ritonavir antiviral drug is successfully used along with other drugs for HIV/AIDS and virus hepatitis C therapy [20–23]. Proserin and biserin drugs, where urethane fragment is combined with quaternized nitrogen atom, can reversibly block cholinesterase [24,25]. They are effective muscle relaxants of peripheral action and are employed in therapy of myasthenia, motor impairment after brain injury, as well as in the recovery period after meningitis, poliomyelitis, encephalitis, and paralysis. Meanwhile, despite the high biotechnological opportunity little information is available on the amphiphilic analogues of these compounds;

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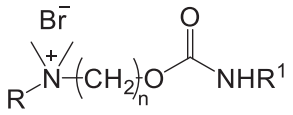
it would be anticipated that the introduction of lipophilic substituents could facilitate drug transport. To compensate this, herein, a series of new alkylammonium cationic surfactants containing urethane fragment with a varying length of hydrocarbon tail and the structure of head group was synthesized and characterized. Formulae of the compounds are given below:



$14Q^+-2-Ur-4$: R = $C_{14}H_{29}$, R^1 = C_4H_9, *n* = 2; **$16Q^+-2-Ur-4$:** R = $C_{16}H_{33}$, R^1 = C_4H_9, n = 2; **$18Q^+-2-Ur-4$:** R = $C_{18}H_{37}$, R^1 = C_4H_9, n = 2; **$16Q^+-2-Ur-2$:** R = $C_{16}H_{33}$, R^1 = C_2H_5, n = 2; **$16Q^+-3-Ur-4$:** R = $C_{16}H_{33}$, R^1 = C_4H_9, *n* = 3.

2. Materials and methods

2.1. Materials

Commercially available Orange OT, pyrene, dipalmitoylphosphatidylcholine (DPPC), dimethylaminoethanols, hexadecyl bromides, butyl isocyanate, ethyl isocyanate, diazobicyclooctane (DABCO) (Sigma, 99%) were used without preliminary purification. All solutions were prepared with double-distilled water purified by Direct-Q 5 UV apparatus; the water resistivity was 18.2 MΩ·cm at 25 °C. Experimental temperatures were maintained at 25 ± 0.1 °C, unless otherwise indicated. All experiments were accurate within 4%.

2.2. Syntheses

The carbamates under study are prepared by the reaction of alkylammonium surfactant containing hydroxyethyl (or hydroxypropyl) substituent at head group with butyl isocyanate (or ethyl isocyanate) using DABCO as a catalyst. The scheme of the process and synthetic details are given on the example of the synthesis of N-[2-((butylcarbamoyl)oxy)ethyl]-*N*,*N*-dimethylhexadecaneammonium bromide (**$16Q^+$-2-Ur-4**) (see Scheme 1):

1 stage. Dimethyl(2-hydroxyethyl)hexadecylammonium bromide has been obtained through the reaction of dimethylaminoethanols and hexadecyl bromides in accordance with [26].

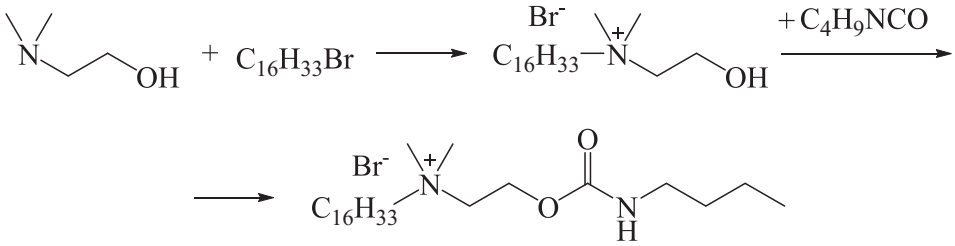
2 stage. The mixture of 3 g (0.0076 mol) of dimethyl(2-hydroxyethyl)hexadecylammonium bromide and 2.26 g (0.022 mol) of butyl isocyanate in 20 mL of acetonitrile was stirred in the flask equipped with a reflux condenser for 2 h at 55 °C. A total of 0.01 g (0.09 mmol) of 1,4-diazabicyclo[2.2.2]octane was used as catalyst. Upon completion of the reaction, volatile components were removed under vacuum. Dry residue was recrystallized twice from ethylacetate and dried under vacuum up to a constant weight; yield was 2.45 g (65%); mp 73–75 °C. The structure of the compounds was confirmed by elemental analysis, ESI mass spectrum, IR- and NMR-spectroscopy data.

N-[2-((butylcarbamoyl)oxy)ethyl]-*N*,*N*-dimethyltetradecaneammonium bromide (14Q^+-2-Ur-4) Yield 65%, mp 58–59 °C. IR spectrum, (KBr), *ν*, cm^{-1}: 3236, 2921, 2853, 1720, 1526, 1471, 1375, 1246, 1140, 1061, 975, 947, 721. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*/Hz): 0.85–1104 m [6H, {N(H)$CH_2CH_2CH_2\underline{CH_3}$ + $N^+CH_2(CH_2)_{11}CH_2\underline{CH_3}$}], 1.25–1.41 m [24H, {$N^+CH_2(\underline{CH_2})_{11}CH_2CH_3$ + $N(H)CH_2CH_2\underline{CH_2}CH_3$}], 1.47–1.54 m [2H, N(H)$CH_2\underline{CH_2}CH_2CH_3$], 1.73 s [2H, $N^+CH_2(CH_2)_{11}\underline{CH_2}CH_3$], 3.17 m (2H, N-$^+CH_2\underline{CH_2}OC$ = O), 3.47 s [6H, $N^+(\underline{CH_3})_2$], 3.61 s [2H, N(H)$\underline{CH_2}CH_2CH_2CH_3$], 3.95 s [2H, $N^+\underline{CH_2}(CH_2)_{11}CH_2CH_3$], 4.54 s (2H, N-$^+\underline{CH_2}CH_2OC$ = O), 6.07 bd.s [1H, N(H)$CH_2CH_2CH_2CH_3$]. ESI mass spectrum, *m*/*z*: 385.5 $[M\text{-}Br]^+$. Found, %:C 59.50; H 10.72; N 6.52; Br 16.58. $C_{23}H_{49}N_2O_2Br$. Calculated, %: C 59.33; H 10.61; N 6.02; Br 17.16. *M* 465.6.

N-[2-((butylcarbamoyl)oxy)ethyl]-*N*,*N*-dimethylhexadecaneammonium bromide (16Q^+-2-Ur-4) Yield 65%, mp 73–75 °C. IR spectrum, (KBr), *ν*, cm^{-1}: 3236, 2920, 2852, 1720, 1526, 1471, 1378, 1246, 1140, 1060, 969, 947, 721. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*/Hz): 0.88–0.94 m [6H, {N(H)$CH_2CH_2CH_2\underline{CH_3}$ + $N^+CH_2(CH_2)_{13}CH_2\underline{CH_3}$}], 1.27–1.37 m [28H, {$N^+CH_2(\underline{CH_2})_{13}CH_2CH_3$ + $N(H)CH_2CH_2\underline{CH_2}CH_3$}], 1.51–1.54 m [2H, N(H)$CH_2\underline{CH_2}CH_2CH_3$], 1.75 s [2H, $N^+CH_2(CH_2)_{13}\underline{CH_2}CH_3$], 3.17 tr (2H, N-$^+CH_2\underline{CH_2}OC$ = O, *J* 6.67 Hz), 3.49 s [6H, $N^+(\underline{CH_3})_2$], 3.60 c [2H, N(H)$\underline{CH_2}CH_2CH_2CH_3$], 3.97 s [2H, $N^+\underline{CH_2}(CH_2)_{13}CH_2CH_3$], 4.56 s (2H, N-$^+\underline{CH_2}CH_2OC$ = O), 5.98 bd.s [1H, N(H)$CH_2CH_2CH_2CH_3$]; ESI mass spectrum, *m*/*z*: 413.5 $[M\text{-}Br]^+$. Found, %:C 60.50; H 10.14; N 5.28; Br 16.12. $C_{25}H_{53}N_2O_2Br$. Calculated, %: C 60.83; H 10.82; N 5.67; Br 16.19. *M* 493.6.

N-[2-((butylcarbamoyl)oxy)ethyl]-*N*,*N*-dimethyloctadecaneammonium bromide (16Q^+-2-Ur-4) Yield 79%, mp 70–72 °C. IR spectrum, (KBr), *ν*, cm^{-1}: 3236, 2919, 2851, 1720, 1526, 1401, 1375, 1247, 1140, 1060, 973, 947,853, 721. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*/Hz): 0.86–0.94 m [6H, {N(H)$CH_2CH_2CH_2\underline{CH_3}$ + $N^+CH_2(CH_2)_{15}CH_2\underline{CH_3}$}], 1.25–1.37 m [32H, {$N^+CH_2(\underline{CH_2})_{15}CH_2CH_3$ + $N(H)CH_2CH_2\underline{CH_2}CH_3$}], 1.50–1.55 m [2H, N(H)$CH_2\underline{CH_2}CH_2CH_3$], 1.74 s [2H, $N^+CH_2(CH_2)_{15}\underline{CH_2}CH_3$], 3.13–3.18 m (2H, $N^+CH_2\underline{CH_2}OC$ = O), 3.48 c. [6H, $N^+(\underline{CH_3})_2$], 3.57–3.62 m [2H, N(H)$\underline{CH_2}CH_2CH_2CH_3$], 4.15 s [2H, $N^+\underline{CH_2}(CH_2)_{15}CH_2CH_3$], 4.54 s (2H, N-$^+\underline{CH_2}CH_2OC$ = O), 6.02 bd.s [1H, N(H)$CH_2CH_2CH_2CH_3$]. ESI mass spectrum, *m*/*z*: 441.6 $[M\text{-}Br]^+$. Found, %:C 62. 75; H 10.60; N 5.68; Br 14.98. $C_{27}H_{57}N_2O_2Br$. Calculated, %: C 62.19; H 11.02; N 5.37; Br 15.32. *M* 521.5.

N-[2-((ethylcarbamoyl)oxy)ethyl]-*N*,*N*-dimethylhexadecaneammonium bromide (16Q^+-2-Ur-2) Yield 78%, mp 75–76 °C. IR spectrum, (KBr), *ν*, cm^{-1}: 3231, 2923, 2852, 1718, 1541, 1468, 1377, 1263, 1158, 1068, 996, 905, 778, 722. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*/Hz): 0.88 t [3H, $N^+CH_2(CH_2)_{13}CH_2\underline{CH_3}$, *J* = 6.9]; 1.19–1.15 t [3H, N(H)$CH_2\underline{CH_3}$, *J* = 7.2], 1.36–1.26 m [26H, $N^+CH_2(\underline{CH_2})_{13}CH_2CH_3$]; 1.74 [m, 2H, $N^+CH_2(CH_2)_{13}\underline{CH_2}CH_3$]; 3.25–3.18 m [2H, N(H)$\underline{CH_2}CH_3$]; 3.48 s [6H, $N^+(\underline{CH_3})_2$]; 3.62–3.58 m [2H, $N^+\underline{CH_2}(CH_2)_{13}CH_2CH_3$]; 3.97 s [2H, $N^+\underline{CH_2}CH_2OC$ = O]; 4.55 s [2H, N-$^+CH_2\underline{CH_2}OC$ = O]; 6.03 s [1H, N(H)$\underline{CH_2}CH_3$]; ESI mass spectrum, *m*/*z*:



Scheme 1. The scheme of the synthesis of the carbamate-bearing surfactant **$16Q^+$-2-Ur-4**.