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Synthesis, biological evaluation and structure-activity relationships of self-assembled and solubilization properties of amphiphilic quaternary ammonium derivatives of quinuclidine

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ABSTRACT

This work deals with development of polyfunctional biocompatible cationic surfactant systems based on bioactive saturated bicyclic alkaloid quinuclidine. It is focused on the effect of the chemical structure of surfactants on their aggregation behavior, their physicochemical estimation of solubility of model water insoluble dye Orange OT and drugs, quercetin and rutin, microbiology and cytotoxicity. Quaternary ammonium derivatives of quinuclidine (Q-Nuc-n) with different hydrophobicity ($R = C_nH_{2n+1}$, where $n = 14, 16, 18$) were synthesized. Self-assembly of Q-Nuc-n was investigated by tensiometry, conductometry, spectrophotometry, fluorimetry and dynamic light scattering. The critical micelle concentration, thermodynamic and adsorption parameters at water-air interface, size and aggregation numbers of Q-Nuc-n micelles were determined. The looser packing of surfactant molecules in Q-Nuc-n micelles compared to its analogues, quaternized derivatives of 1,4 diazabicyclo[2.2.2]octane (DABCO-n), was established. The hydrophobic dye Orange OT and drugs quercetin and rutin were solubilized in micellar Q-Nuc-n solutions better than in solutions of classical surfactant CTAB and its analogue DABCO-n. Solubilization capacity of Q-Nuc-18 is 5 times higher than that of classical surfactant CTAB. Q-Nuc-18 1.95 $\mu g \cdot mL^{-1}$ has also bactericidal and fungicidal activity 2 times (against *S. aureus 209P*) and 8 times (against *B. cereus 8035*) higher than antibiotics Norfloxacin and antifungal Ketoconazole. Q-Nuc-16 has the highest bactericidal activity. It is 6 times (against *S. aureus 209P*) and 15 times (against *B. cereus 8035*) higher than the bactericidal activity value of Norfloxacin. Synthesized cationic surfactants based on quinuclidine are new multifunctional biocompatible compounds with high potential in nanomedicine and biotechnology.

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1. Introduction

Nowadays the development of new multifunctional biocompatible compounds is demanded not only in industry, but also in nanomedicine and biotechnology. The supramolecular structures organized by amphiphilic compounds in solution (micelles, vesicles, bilayers, etc.) have different useful properties (adsorption, catalytic activity, solubilization etc.) [1–3]. New amphiphilic compounds and supramolecular systems play an important role in the discovery of new classes of targeted drug delivery carriers [4] and gene delivery agents [5,6]. Also, modification of commonly used nanocarriers by new amphiphilic compounds improves the characteristics and properties of nanosystems, for example, to make possible crossing of biological barriers. Due to sensitivity to various factors (temperature, pH, light, magnetic and electric fields), surfactants are very attractive for creation of nanosystems with controlled properties [7–10]. The biomimetic approach was able to enhance new biocompatible surfactants with a low critical micellar concentration (gemini surfactants) [11,12], polycationic amphiphiles [13,14], amphiphiles with natural fragments, such as sugar- [15,16], peptide- [17,18], pyrimidine- [19] containing surfactants. Environmental safety and improving the efficiency of surfactants are implemented in synthesis strategy of amino acids surfactants [20,21]. The structure of bioactive quinuclidine molecule makes it possible to combine biological activity and therapeutic action, and it is capable of creating nanocarriers at the same time [22]. Many effective therapeutic agents were synthesized in medicinal chemistry using saturated bicyclic alkaloid quinuclidine as a

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pharmacophore [23–25]. Quinuclidine derivatives have a wide spectrum of antibacterial [26,27] and in vitro antioxidant [28] properties. They have been identified as potent M3 muscarinic antagonists [29] and agonists of α7 nicotinic acetylcholine receptors [30]. They improve cognitive functions in experimental animal models, oral bioavailability, and brain penetration with perspectives for treatment of central nervous system diseases [31]. At the same time, they could form nanoassemblies, displaying biological and therapeutic activity. In this respect, this study deals with new quaternized derivatives of quinuclidine (Q-Nuc-n, where R = C_nH_{2n+1}, n = 14, 16, 18). The goal of this work was to establish the relationship between surfactants structure, morphology and aggregation number of micelles and their solubilizing properties toward a poorly water soluble dye (Orange OT) and drugs (quercetin and rutin). The influence of Q-Nuc-n structure (head group and the chain length of surfactant) on the properties was considered and compared with its analogues (Fig. 1). The development of new surfactants containing these bicyclic moieties is focused in our group.

2. Experimental

2.1. Materials

1 Azabicyclo[2.2.2]octane (97%, quinuclidine, Aldrich, Saint Louis, USA), 1 bromotetradecane(98%, NJ, USA, Acros), 1 bromohexadecane (97%, NJ, USA, Acros), 1 bromooctadecane (96%, NJ, USA, Acros), cetyltrimethylammonium bromide (CTAB, 99%, DK, Acros) were used as received; quaternized derivatives of 1,4 diazabicyclo[2.2.2]octane (DABCO-n) were synthesized as described earlier [32], 1 (*o* Tolylazo) 2 naphthol (75%, Orange OT, Aldrich, USA), pyrene (99%, Sigma, Switzerland), cetylpyridinium bromide (CPB, 99.2%, AppliChem, BioChemica, Darmstadt, Germany), Quercetin (≥95% (HPLC), solid, Sigma–Aldrich, India), Rutin (97%, CN, Acros) were used as received.

2.2. Synthesis of Q-Nuc-n

Tetradecyl quaternized derivative of 1 azabicyclo[2.2.2]octane (quinuclidine) (Q-Nuc-14) was prepared by the reaction of quinuclidine (0.5 g, 4.49 mol) with 1 bromotetradecane (1.49 g, 5.37 mol) in acetone (30 cm^3) at boiling acetone temperature during 10 h. The precipitated salt filtered off, recrystallized from acetone, and dried in vacuo.

Compounds (Q-Nuc-16, Q-Nuc-18) were synthesized according to a similar procedure with recrystallization from an acetone.

2.3. Characterization of Q-Nuc-n

2.3.1. 1 Tetradecyl 1 azoniabicyclo[2.2.2]octane bromide (Q-Nuc-14)

The product was obtained in a yield of 1.31 g (75%), m.p. 229–230 °C. IR (KBr), υ/cm^{-1}: 2920, 2850, 1471, 1380, 1103, 1046, 965, 929, 843, 725. ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3H, $N^+CH_2CH_2(CH_2)_{11}\underline{CH_3}$, J = 6.7 Hz); 1.22–1.36 (m, 22H, $N^+CH_2CH_2(\underline{CH_2})_{11}CH_3$); 1,76 (2H, br. $N^+CH_2\underline{CH_2}(CH_2)_{11}CH_3$); 2.09 (s, 6H,$CH(\underline{CH_2})_3$); 2.25 (m, 1H, $\underline{CH}(CH_2)_3$), 3.47 (m, 2H, $N^+\underline{CH_2}CH_2(CH_2)_{11}CH_3$); 3.74 (t, 6H, $N^+(\underline{CH_2})_3$, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 64.53, 54.87, 31.89, 29.64–29.25, 26.46, 24, 06, 22.65, 22.55, 19.54, 14.07. Calculated %: C 64.92; H 10.89; N 3.60; Br 20.57; Found %: C 64.75; H 11.32; N 3.80; Br 20.79. ESI MS, *m/z*: 308.5 $[M\text{-}Br]^+$.

2.3.2. 1 Hexadecyl 1 azoniabicyclo[2.2.2]octane bromide (Q-Nuc-16)

The product was obtained in a yield of 1.55 g (83%), m.p. 238–239 °C. IR (KBr), υ/cm^{-1}: 2918, 2850, 1472, 1381, 1102, 1040, 963, 928, 843, 720. ^{1}H NMR ($CDCl_3$), δ: 0.88 (t, 3H, $N^+CH_2CH_2(CH_2)_{13}\underline{CH_3}$, J = 6.9 Hz); 1.25–1.34 (m, 26H, $N^+CH_2CH_2(\underline{CH_2})_{13}CH_3$); 1,72 (2H, br. $N^+CH_2\underline{CH_2}(CH_2)_{13}CH_3$); 2.07 (s, 6H, $CH(\underline{CH_2})_3$); 2.22 (m, 1H, $\underline{CH}(CH_2)_3$), 3.46–3.48 (m, 2H, $N^+\underline{CH_2}CH_2(CH_2)_{13}CH_3$); 3.73 (t, 6H, $N^+(\underline{CH_2})_3$, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 64.54, 54.88, 31.89, 29.67–29.32, 26.46, 24.05, 22.65, 22.53, 19.53, 14.07. Calculated %: C 66.32; H 11.13; N 3.36; Br 19.18; Found %: C 65.95; H 11.41; N 3.45; Br 19.14. ESI MS, *m/z*: 336.5 $[M\text{-}Br]^+$.

2.3.3. 1 Octadecyl 1 azoniabicyclo[2.2.2]octane bromide (Q-Nuc-18)

The product was obtained in a yield of 1.75 g (88%), m.p. 239–240 °C. IR (KBr), υ/cm^{-1}: 2918, 2850, 1472, 1381, 1102, 1040, 963, 928, 843, 720. ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3H, $N^+CH_2CH_2(CH_2)_{15}\underline{CH_3}$, J = 6.9 Hz); 1.19–1.34 (m, 30H, $N^+CH_2CH_2(\underline{CH_2})_{15}CH_3$); 1,72 (2H, br. $N^+CH_2\underline{CH_2}(CH_2)_{15}CH_3$); 2.08 (s, 6H, CH $(\underline{CH_2})_3$); 2.23 (m, 1H, $\underline{CH}(CH_2)_3$), 3.44–3.48 (m, 2H, $N^+\underline{CH_2}CH_2(CH_2)_{15}CH_3$); 3.71 (t, 6H, $N^+(\underline{CH_2})_3$, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 64.48, 54.83, 31.89, 29.68–29.25, 26.45, 24.04, 22.65, 22.54, 19.54, 14.07. Calculated

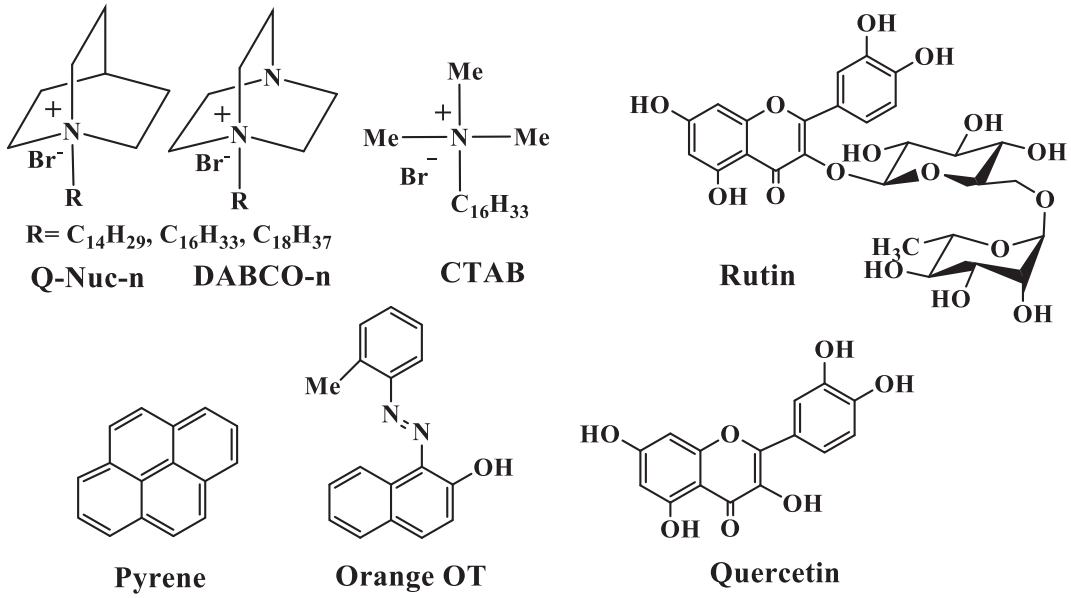

Fig. 1. Structures of quinuclidine (Q-Nuc-n) and 1,4 diazabicyclo[2.2.2]octane (DABCO-n) quaternized derivatives, Orange OT, Pyrene, Quercetin, Rutin, cetyltrimethylammonium bromide (CTAB).

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