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Spectrophotometric study of quercetin in metallomicellar solutions of 1-hexadecyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide complex with copper dibromide

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ABSTRACT

The influence of 1-hexadecyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide (D-16) complex with copper dibromide ([D-16 × $CuBr_2$]) on the solubility of quercetin has been investigated by spectrophotometric method. High solubilization activity of the system in both premicellar and post-critical micelle concentration (CMC) ranges of complex concentrations was found. Analysis of spectral data strongly supports the interaction of metallosurfactant with quercetin and testifies the partial modification of the drug, including the complexation of quercetin with a copper cation below and above the CMC and the oxidation of the drug in micellar solutions. Solubilization of the drug in [D-16 × $CuBr_2$] micelles is accompanied by changes in size behavior of aggregates of the complex.

1. Introduction

Supramolecular systems based on surface-active agents (surfactants) are considered as biomimetic systems and attract research interest in the fields of chemistry, biology and pharmacy. They are widely used to fabricate new materials, to solve environmental problems, to develop green chemistry technologies, etc. Inclusion of transition metal into amphiphilic molecules may considerably modify their functional activity [1], which is of particular importance in biomedical applications [2–4]. Meanwhile before supramolecular systems may be approved for practical applications they need to be comprehensively characterized in terms of physico-chemical parameters. This would provide fundamental basis for the further examination of their practical potential in modern technologies. In our studies a variety of surfactants has been explored, with special attention paid to homological series of cationic amphiphiles [5–8]. For these series, aggregation properties, solubilization capacity, complexation with DNA, catalytic and antimicrobial effects were examined. Data obtained are of importance from the viewpoints of information resource for the comparison of key characteristics responsible for the functional activity. Besides, they provide rational for choosing the composition of formulations for the solution of practical tasks.

Mono- and dicationic surfactants, derivatives of 1,4-diazabicyclo[2.2.2]octane (DABCO) are reported to show aggregation activity similar to typical cationic surfactants with trimethyl ammonium (TMA) head groups [9–12], in particular, critical micelle concentration (CMC) of hexadecyl homologues DABCO (D-16) (Scheme 1) and cetyl trimethyl ammonium bromide (CTAB) are identical [9]. Meanwhile DABCO based surfactants are characterized by essential benefits from the viewpoint of potential technological applications over TMA series due to (i) diverse morphological behavior, which can be developed toward superamphiphilic performance by combination with calixarene platform [13,14]; (ii) higher solubilization capacity [15,16]; (iii) high catalytic effect, which can be modified by noncovalent conjugation with the calixarene or polymer matrixes [17–20]; (iv) marked antimicrobial activity [10]; (v) lower toxicity, which can be further diminished by addition of nontoxic hydrotropic additives [21]; (vi) presence of electronic donor center capable of complexing with metal ions, thereby enhancing aggregation and functional activity of DABCO surfactants [22,23]. We are aware that dynamic systems like micelles are strictly limited for in vivo application. Meanwhile micelles loaded with drugs and probes can be used as a matrix for the further fabrication of more stable nanocontainers and capsules [24].

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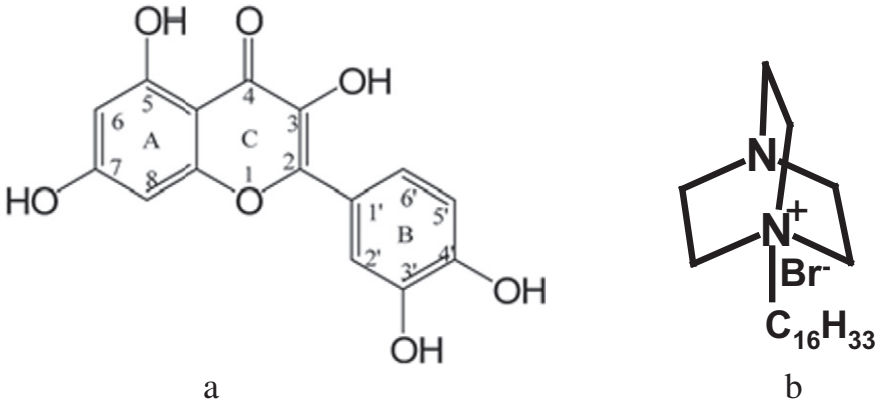

Scheme 1. Structural formulas of quercetin (a) and D-16 (b).

Micellar systems and microemulsions are known to attract much attention as nanocontainers for hydrophobic guests due to their significant impact on the solubility of hydrophobic compounds [7,16]. Incorporation of biologically active compounds especially drugs into amphiphilic aggregates is a promising way to increase their bioavailability and biocompatibility [16,25]. Moreover, the solubilization of probes and drugs in micellar systems may be accompanied by the modification of solubilizates (e.g. by changes in acid-base properties of drugs [26–31]), which may provide beneficial effect, shifting the equilibria toward the more active form. Present study focuses on spectrophotometry monitoring of 3,3′,4′,5,7-pentahydroxyflavone, quercetin (Scheme 1) in micellar solution of D-16 based metallosurfactant. Quercetin is a polyphenol belonging to a class of bioflavonoids, showing antioxidant, anticancer, antiinflammatory, antispasmodic, antiulcerogenic, diuretic, and antisclerotic effects [32–34]. It is slightly soluble in ethanol and practically insoluble in water [32,34], while it may by effectively solubilized in micellar systems [21,26]. Previously, we report on the ability of D-16 and its mixture with *N*-methyl-D-glucamine (MG) of increasing the water solubility of quercetin [21]. In the present work, we studied the influence of the complex of D-16 with copper dibromide on the solubility of quercetin in water. Complex [D-16 × $CuBr_2$], with the 1:1 molar ratio of ligand (D-16) to the cation copper(II), demonstrated amphiphilic properties, e.g. it is capable of forming the micellar aggregates in aqueous solution [22]. The CMC values of the complex at 25 °C are 0.65 mM (tensiometry) and 0.61 mM (conductometry), which is approximately twice lower than the CMC of the ligand (D-16) equal to 1 mM [9]. The value of solubilization capacity of D-16/Cu(II) complex toward the water-insoluble dye Orange OT is by 20–30% higher compared to single D-16 and threefold higher than that of conventional cationic surfactant CTAB. Furthermore, D-16/Cu(II) complex showed superior antifungistatic, antibactericidal and antifungicidal activity over D-16 and CTAB for some strains [22]. These findings encourage us to explore the metallosurfactant focusing on the solubilization capacity toward biologically active compounds, in particular quercetin.

2. Materials and methods

2.1. Chemicals

Synthesis of the complex of D-16 with copper dibromide in methanol was performed according to the method [22]. Quercetin (≥95%, (HPLC), solid, Sigma-Aldrich, Saint Louis, USA) was used. Water purified using a Direct_Q 5 UV system (Millipore S.A.S., Molsheim-France) was used for the preparation of solutions. The content of dissolved oxygen determined by analyzer SG6 (Series Seven Go™, Metter Toledo Instruments, Switzerland) was 8.15–9.0 mg/l.

2.2. Methods

2.2.1. UV–vis spectroscopy

Electronic absorption spectra of solutions were recorded on Specord 250 Plus spectrophotometer (Analytik Jena AG, Germany) in the wavelength range 190–1100 nm at a temperature of 25 ± 0.01 °C using thermostatted quartz cuvettes (1.0, 0.5, 0.1 cm). The accuracy of absorbance measurements was ± 1%.

2.2.2. Drug solubilization study

The preparation of solutions of the complex with the drug was performed as follows. The powder of quercetin was put in 5 ml metallosurfactant solution (at 0.002 g of the drug per 1 ml of solution), intensively stirred for 1 h and kept for three days to achieve the maximum dissolution and allow the system to equilibrate. The resulting solutions were passed through Millipore Millex filters (0.45 μm). Spectra of solutions of the complex with the drug were fixed relative to reference solutions of the complex of the same concentration without quercetin. Solutions with the lowest concentration of quercetin was obtained introducing appropriate amount of quercetin solution in methanol (2 mM) by microsyringe in aqueous micellar solution of the complex or D-16.

2.2.3. Dynamic light scattering

The particle sizes were determined with the use of the Malvern Instrument Zetasizer Nano system for characterization of nanoparticles (UK). A He-Ne gas laser with the wavelength 633 nm served as a laser radiation source. The measured autocorrelation functions were analyzed by Malvern DTS software, and the second-order cumulant expansion method. The determination of particle sizes was performed according to the Stokes-Einstein equation for spherical particles. The effective hydrodynamic diameter was measured at least three times for each sample. The average error in these experiments was approximately 4%.

3. Results and discussion

Fig. 1 shows the absorption spectra of quercetin in aqueous solutions of the complex [D-16 × $CuBr_2$] (samples with the drug were aged for 3 days).

As can be seen the differences occur between the spectra of micellar and premicellar solutions. The absorption spectrum of the drug within metallosurfactant concentrations of 0.6 to 0.7 mM has three absorption bands with similar optical density. The first band has a maximum at 260 nm that shifts to 270 nm with an increase in the concentration. The second and third bands have maximum at 361 nm and 418 nm, respectively. Absorption bands at 274 nm, 300 nm, 365 nm, and a