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Aqueous mixtures of di-*n*-decyldimethylammonium chloride/polyoxyethylene alkyl ether: Dramatic influence of tail/tail and head/head interactions on co-micellization and biocidal activity

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ABSTRACT

Mixed aggregate formation and synergistic interactions of binary surfactant mixtures of di-*n*-decyldimethylammonium chloride, **[DiC$_{10}$][Cl]**, with polyoxyethylene alkyl ethers, **C$_i$E$_j$** (i = 10, 12, j = 4, 6, 8), have been investigated for various **[DiC$_{10}$][Cl]**/**C$_i$E$_j$** ratios. The critical aggregation concentration of the binary mixtures has been determined by tensiometry, and the aggregate characteristics (i.e., size and composition, free ammonium concentration) have been estimated using the pulsed field gradient NMR spectroscopy and a **[DiC$_{10}$]**-selective electrode. Diffusion coefficient measurements of micelles confirmed the synergistic interaction between the surfactants. It is thus shown that the formation of surface monolayers and mixed aggregates from **[DiC$_{10}$][Cl]**/**C$_{10}$E$_j$** mixtures is driven by both tail/tail and head/head interactions, whereas **[DiC$_{10}$][Cl]**/**C$_{12}$E$_j$** co-aggregation is mainly driven by tail/tail interactions. As a consequence, the co-aggregation phenomenon notably influences the biocidal activity of **[DiC$_{10}$][Cl]** on the *Candida albicans* fungi. In the presence of **C$_{12}$E$_j$**, the biocidal activity of the ammonium salt is inhibited due to the trapping of the cationic surfactants in the mixed aggregates, whereas in the presence of **C$_{10}$E$_j$**, the biocidal activity of the surfactant mixture is maintained. The mode of action is also confirmed by a faster increase in the zeta potential of a *C. albicans* suspension in the presence of **[DiC$_{10}$][Cl]**/**C$_{10}$E$_8$** than in the presence of **[DiC$_{10}$][Cl]**/**C$_{12}$E$_8$**. Therefore, a judicious adjustment of the alkyl (i) and polyoxyethylene (j) chain lengths of **C$_i$E$_j$** avoids its antagonistic effect on the biocidal activity of **[DiC$_{10}$][Cl]**.

1. Introduction

Surfactant mixtures are used in a large variety of industrial and commercial applications since they generally exhibit superior performances resulting from better interfacial characteristics than individual surfactants. Actually, in most cases, binary surfactant systems exhibit synergism both in surface tension reduction and in mixed micelle formation [1]. Such synergetic effects are important for a wide range of surfactant-based phenomena such as foaming, emulsification, solubilization, and detergency. Hence, knowledge of the aqueous behavior of ionic–nonionic surfactant mixtures is thus important from both theoretical and practical applications as they exhibit nonideal behavior on mixing.

Double-tailed cationic surfactants such as didecyldimethylammonium chloride, abbreviated as **[DiC$_{10}$][Cl]**, are well-known biocidal agents [2–6], whereas nonionic polyoxyethylene alkyl ethers, noted **C$_i$E$_j$**, where i represents the alkyl chain length and j the number of ethylene oxide units, are often used for their detergent solubilizing, emulsifying, or wetting properties [7]. However, the combination of both these surfactants in detergent–disinfectant formulations can lead to important modifications of the individual physicochemical properties and the biocidal or detergent activity may be altered. Hence, a better understanding of their interaction and of the co-micellization process is necessary.

In aqueous solution, dialkyldimethylammonium surfactants **[DiC$_n$]** with n = 16–18 self-assemble into predominantly planar structures (bilayers or vesicles) characterized by a low or zero spontaneous curvature [8–12]. The same behavior can be observed with smaller homologous (e.g., **[DiC$_{10}$]**, **[DiC$_{12}$]**, and **[DiC$_{14}$][Br]**) since their packing parameter ($p = v/al$) is close to 0.62 [13]. As an example, **[DiC$_{12}$][Br]** forms stable aggregates in the form of flexible bilayers or unilamellar vesicles [14]. In contrast, **C$_i$E$_j$** surfactant aggregates can have a range of spontaneous curvatures, from planar to highly curved aggregated structures, depending on the

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polyoxyethylene chain length and on the ratio of alkyl to ethylene oxide chain length [15,16].

The behavior of mixed surfactant systems in aqueous solution has extensively been studied [17–20]. However, binary mixtures of short-chain dialkyldimethylammonium cationic/polyoxyethylene alkyl ether nonionic surfactants are much less documented, and most reported studies on **[DiC$_n$]/C$_i$E$_j$** systems mainly deal with long alkyl chain ammonium salts (typically $n \geqslant 16$) [8–12,21,22]. Moreover, beyond the physicochemical behavior of the binary surfactant systems, it is relevant to establish some relationships with the application properties.

In this context, we have investigated different surfactant binary systems based on polyoxyethylene decyl and dodecyl ethers **C$_i$E$_j$** (with $i = 10$ or 12 and $j = 4$, 6, 8) and di-*n*-alkyldimethylammonium chloride **[DiC$_n$][Cl]** (with $n = 6$, 8, 10, or 12) as nonionic and double-tailed cationic surfactants, respectively. As the biocidal mechanism is not clearly established for **[DiC$_n$][Cl]** salts, especially on fungi, we report on a detailed study of the structure–activity relationships. *Candida albicans*, as a potentially commensal pathogenic diploid fungus, has been chosen for the study. It is actually responsible for opportunistic oral and genital infections in humans [23]. Systemic fungal infections have emerged as important causes of morbidity and mortality in immunocompromised patients (AIDS, chemotherapy, etc.). In addition, hospital-related infections in patients not previously considered at risk (i.e., patients in an intensive care unit) have become a cause of major health concern [24]. To prevent nosocomial infections, hospitals have sanitation protocols regarding uniforms, equipment sterilization, washing, and other preventative measures. Hence, many detergent–disinfectant formulations based on surfactant mixtures are used to clean chirurgical instruments, and control of the biocidal activity is of high importance.

We also focus our attention on **[DiC$_{10}$][Cl]** because it is the most bioactive salt and it is the archetypal model of surfactants used in numerous commercial detergent–disinfectant formulations. The Rubingh model and PGSE NMR (Pulsed Gradient Spin-Echo) spectroscopy have been used to explore the composition and the physicochemical properties of various **[DiC$_{10}$][Cl]/C$_i$E$_j$** surfactant ratios. As the interaction between the cationic and the nonionic surfactants strongly influences the biocidal activity, the relationship between co-aggregation and biocidal activity has been investigated. Our approach has consisted in determining the concentration of nonaggregated molecules of **[DiC$_{10}$]** with a home-made selective electrode and correlated with the biocidal activity. Finally, the biocidal mechanism has been investigated by the measurements of the zeta potential of a *C. albicans* suspension as a function of **[DiC$_{10}$][Cl]** concentration and time for **[DiC$_{10}$][Cl]/C$_{10}$E$_8$** and **[DiC$_{10}$][Cl]/C$_{12}$E$_8$** mixtures.

2. Experimental section

2.1. Materials and general information

Well-defined polyoxyethylene alkyl ethers **C$_i$E$_j$** with $i = 10$, 12 and $j = 4$, 6, 8 were purchased from TCI. Their purity, in terms of both alkyl chain length and ethylene oxide distribution, was higher than 99.9%. The other reagents were purchased from Sigma–Aldrich chemicals and used without further purification. Pure di-*n*-alkyl-dimethylammonium chloride (**[DiC$_n$][Cl]**, $n = 6$, 8, 10, 12) was synthesized according to the procedure described in our previous work [25]. Each surfactant mixture was prepared extemporaneously by mass, and the total surfactant concentration was fixed. The resulting solution was diluted for surface tension. For more information, see ESI.

2.2. Biocidal activity determination

The minimum biocidal concentration (MBC) was determined according to the European Standard NF EN 13 624 (2004): quantitative suspension test for the evaluation of fungicidal activity of chemical disinfectants for instruments used in medicine. A sample of the product as delivered and/or diluted with water was added to a test suspension of yeast cells with interfering substances (mixture of bovine albumin solutions with sheep erythrocytes). The number of yeast cells in the suspension was adjusted between 1.5 and 5.0×10^7 cfu/mL. The mixture was maintained at 20 ± 1 °C for 15 min ± 10 s. At the end of this contact time, an aliquot was taken; the biocidal activity in this portion was immediately neutralized or suppressed by dilution/neutralization method. The number of surviving yeasts in each sample was determined, and the reduction was calculated and expressed in logarithm. The reduction was defined as the ratio between the number of cfu/mL in the test suspension at the beginning of the contact time and the number of survivors per mL. For each test, the lowest concentration of ammonium that does not support colony formation is defined as the MBC. The test was performed using *C. albicans* ATCC 10231. The product shall be deemed to have passed the NF EN 13 624 standard for biocidal activity if it demonstrates in a valid test at least a 4log reduction in one of the test conditions defined by the European Standard.

2.3. Molecular modeling

All calculations were made on a Windows® platform (Intel® Core2™ Extreme CPU X9770 3.20 GHz). The initial structures of molecules were sketched using Avogadro 0.9.6 [26]. Atom and bond types were adjusted and minimized with the MMFF94 force field parameters. Using the optimized structures, a systematic conformational search on each molecule was performed.

(i) *Octanol–water partition coefficient calculation*. The lowest energy conformation structure, obtained from MMFF94, was optimized with the PM6 method at the restricted Hartree–Fock level (RHF) in aqueous solution (MOPAC2009™) [27]. The aqueous environment was created with a conductor-like screening model (COSMO). A relative permittivity of 78.4 was employed with up to 92 surface segments per atom for the COSMO model being used to construct a solvent accessible surface area based on van der Waals radii. All structures were optimized to a gradient inferior to 0.1 using the eigenvector following method. The Broto octanol–water partition coefficients (log*P*) were evaluated by molecular lipophilicity potential with Vega ZZ [28].

(ii) *Screening charge-density profile*. From the MMFF94 results, the lowest-energy conformation structures were optimized with the PM6 method at the restricted Hartree–Fock level (RHF, MOPAC2009™) [27] until to reach a gradient inferior to 0.1 using the eigenvector following method. The effective radius of solvent is fixed at 1.3 Å. A relative permittivity of 999.0 was employed with up to 92 surface segments per atom. The van der Waals radii are fixed at H = 1.3, C = 2.0, N = 1.83, O = 1.72, P = 2.12, and Cl = 2.05 Å. Using the COSMO information generated by MOPAC, the σ-profiles were obtained after averaging by the COSMO segment activity coefficient model (COSMO-SAC) developed by Lin and Sandler [29]. COSMO-SAC is a refinement of the COSMO-RS model of Klamt [30]. The COSMO-SAC parameters are taken from the original work of Lin and Sandler ($a_{eff} = 7.5$ Å^2, $c_{hb} = 85{,}580$ kcal/mol/Å^4/e^2, and $\sigma_{hb} = 0.0084$ e/Å^2) [29].