Antimicrobial Activity of Gemini Surfactants

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Gemini cationic surfactants (GS) are constructed from two alkylammonium monomeric salts linked by a spacer.They exhibit significant surface, aggregation and antimicrobial properties. Due to the fact that, in order to achieve the desired utility effect, the minimal concentration of compounds are used, they are in line with the principle of greenolution (green evolution) in chemistry. The obtained results indicate that the synthesized compounds are effective microbicides with a broad spectrum of biocidal activity and are active against *Escherichia coli*, *Staphylococcus aureus*, yeast *Candida albicans*, molds *Aspergillus niger* and *Penicillium chrysogenum*. These compounds constitute a new, interesting class of microbicides with a broad spectrum of biocidal activity.

gemini surfactants | antimicrobial activity | MIC | surface activity

1. Introduction

The most important and rapid developing group of antimicrobials includes the quaternary ammonium compounds (QAC).[1] Their effectiveness has been proven over the past century, and various new generations have been introduced since then.[2][3] In the second half of the twentieth century, double quaternary ammonium salts were obtained, and named gemini surfactants (GS) by Menger in 1991.[4] Since then, this class of compounds has been very intensively developed.

These compounds are constructed from two single alkylammonium monomeric salts linked by a connector (spacer). The spacer can be a flexible chain (i.e. polymethylene) or rigid molecule, such as benzene. The linker can also be functionalized by electron-rich atoms, such as oxygen or nitrogen. The substituent is most often a hydrocarbon chain or it can be functionalized by different organic functional groups. The complement to the structure of GS, which ensures the neutral charge of the molecule, is a counter ion.[5][6][7][8][9] The possibility of modifying the structure within the linker, substituents, counter ion, or the cation environment makes it possible to design the structure of the compound so that it exhibits the desired utility properties.

The presence of two cations in the molecule causes gemini surfactants to possess several times better properties than their monomeric counterparts.[10][11][12] They are also known for their broad spectrum of action against bacteria,[13][14] fungi,[15][16] and algae.[17] QAC are significant antiviral compounds[18][19][20]; therefore, it can be assumed that the effectiveness of gemini surfactants against viruses will also be high. The unique antimicrobial activity of gemini surfactants can be explained by the mechanism of biocidal action, which consists in adsorption of cations on the surface of the microorganism and penetration by long alkyl substituents of the cell membrane. This results in damage and outflow of the cytoplasm along with potassium ions and other cellular components, resulting

in the death of the microbial cell.[21][22][23] Gemini surfactants are named as multifunctional because they also show high aggregation, surface, and anticorrosive activity.[24][25][26] Moreover, compared to QAC, they are less toxic with respect to aquatic organisms.[27][28] Gemini surfactants have one more unique features that makes them superior to QAC; they are not susceptible to current QAC bacterial resistance machinery. Due to conformational flexibility, these compounds tend to escape such resistance mechanisms.[29]

2. Development

A very useful and most commonly used parameter for antimicrobial activity of the microbiocides comparison is minimum inhibitory concentration (MIC), i.e., the lowest concentration of compound inhibiting the visible growth of microorganisms after incubation. MIC values depend on several factors: concentration of active agent, time of the contact, pH, temperature, the presence of organic matter or other compounds, as well as nature, numbers, location, and condition of the microorganism. The main factor determining the antimicrobial activity of gemini surfactants is chemical structure. Antimicrobial efficiencies of homologues series of long chain surfactants show a non-linear dependence on chain length. This dependence is quasi parabolic, and named by Devinsky as cut-off effect.[30][31] Such a relationship is characteristic of the homologous series of gemini surfactants: 3-oxa-1,5-pentane-bis(*N*-alkyl-*N,N*-dimethylammonium bromides) (n-O-n),[8] 3-methylaza-1,5-pentane-bis(*N*-alkyl-*N,N*-dimethylammonium) dibromides (n-N-n),[32] or 1,6-hexamethylene-bis(N-alkyl-N,N-dimethylammonium bromides) (n-6-n).[33] Compounds with short alkyl chain show the highest values of MIC, and minimal antimicrobial activity. The substituents are too short to effectively penetrate the outer shell of the microorganism's cells. An increase in hydrocarbon substituent results in an increase in antimicrobial activity (lowering of MIC value). Compound with 12 carbon atoms in substituents proved to be the most active against microorganisms. Further increase in the hydrophobic chain results in a decrease in activity (increasing of MIC value), due to limited solubility in the aqueous. Compounds bearing functionalized spacers by ether (n-O-n) or amine (n-N-n) group show very similar antibacterial and antifungal activity.[8][32] Very close MIC values were also received for 12-6-12. Compounds 12-O-12, 12-N-12 and 12-6-12 have a similar molecular surface. Therefore, it can be concluded that the introduction of an electron-rich group into the spacer does not result in better adsorption of the microbiocide on the surface of the microorganism's cell. Therefore, it does not involve an increase in antimicrobial activity. On the other hand, this GS possess better antibacterial activity than compared to analogic compounds with a stiff spacer constructed from an aromatic ring.[34] Compound 12-Ph-12 shows more than three times higher MIC values against *S. aureus* and *E. coli* than compared to 12-O-12. It is worth emphasizing that the GS show much greater antimicrobial activity than their monomeric counterparts. The MIC values of DTAB (*N*-dodecyl-*N,N,N*-trimethylammonium bromide) are 0.252, 0.36, and 0.5 mM against *S. aureus*, *E. coli*, and *C. albicans*, respectively.[10][35] 12-O-12 proved to be at least 30 times more active than DTAB. The most efficient microbiocide against all tested microorganisms is 12-O-12, which is comparable to the activity of compound 12-6-12. Compound 12-O-12 is a more than 30 times more efficient microbiocide than DTAB. Obtained GS are more active against Gram (+) bacteria than Gram (−) bacteria. These compounds constitute a new, interesting class of microbicides with a broad spectrum of biocidal activity.

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