European Journal of Medicinal Chemistry 44 (2009) 3201–3208

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and antimicrobial properties of polymerizable quaternary ammoniums

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ARTICLE INFO

Article history:
Received 16 July 2008
Received in revised form
13 March 2009
Accepted 19 March 2009
Available online 1 April 2009

Keywords:
Quaternary ammonium compounds
Surfactants
Preservatives
Biocides
Monomers
Surfmers

ABSTRACT

Introduction of biocide monomers during the process of polymerization is a promising approach in the development of new permanent non leaching biocide materials. Two series of surfactants monomers, with a quaternary ammonium group as polar head and an acrylic function as the polymerizable moiety, were synthesized and tested to evaluate their surface active properties alongside with their antibacterial and antifungal properties. Four microbial strains were used to perform the study: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger*. The biocidal efficacy measured by bacterial and fungal growth inhibition expressed as MIC (Minimal Inhibitory Concentration) and MLC (Minimal Lethal Concentration) values was discussed as a function of molecular parameters. All the synthesized surfactant monomers presented bactericidal and fungicidal activities. Increasing the spacer between the acrylic part and the ammonium group has a favourable effect on the MIC and MLC results.

1. Introduction

The battle against nosocomial infections such as, among others, surgical infections, remains one of the major actual challenges of the hospital. If cautions are numerous to avoid any pollution of inert surfaces (catheters, implants, medical equipments, floors…), the phenomena of resistance developed by the most part of pathogenic organisms require, on one hand, the elaboration of new biocide agents and, on the other hand, completion of long-term bactericidal treatments of surfaces or, in an ideal case, a permanent biocide effect of the surfaces without releasing of the antimicrobial active agents. The implementation of biocide polymeric coatings with a permanent effect introduces not negligible advantages: a non release of antibacterial agents in the surrounding environment and, consequently, a reduction of the resistance phenomena with an attenuation of the development of multi resistant germs [1]. As compared with conventional antibacterial agents of low molecular weight, polymeric antibacterial agents have also the advantages to be non volatizable, chemically stable and hard to permeate through the skin. Moreover, increased efficiency, selectivity, and handling safety are additional benefits.

In the field of disinfection, quaternary ammonium surfactants (QAS) are well-known effective antimicrobial agents and are used in a number of domains such as cosmetics, common antiseptics, sanitizers in hospitals and disinfectants for contact lenses [2]. The efficacy of such agents is conditioned by the amphiphilic nature of the molecule [3] and consequently by its surfactant properties [4]. These products possess properties such as reduction of surface tension and a ready attraction for negatively charged surfaces like bacteria. These characteristics promote their adsorption onto bacteria surfaces. Although, the mode of action cannot be reduced to surface activity only, a cytolytic damage is the primary lesion caused by such cationic surfactants and a major contribution to the cell death. Consequently, there is a well-established relationship between cytolytic action and surface tension [5].

In the perspective to elaborate biocide polymeric materials, we therefore chose to synthesize quaternary ammonium surfactants

Abbreviations: CMC, critical micellar concentration; MIC, minimal inhibitory concentration; MLC, minimal lethal concentration; Surfmers, surfactants monomers.

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doi:10.1016/j.ejmech.2009.03.031

with an additional polymerizable acrylic moiety. The synthesized compounds are represented Fig. 1.

Some of this kind of compounds has already been described in literature for their surfactant properties [6–8].

Indeed, surfmers (for SURFactant monoMERS) have been extensively studied [9–14] because their reactive functionalities give to these surfactants the potentiality to control overall material properties as they polymerize into the bulk polymer network [15,16]. They can be charged easily for the incorporation of proper biological ligand [17,18] and controllable drug release [19] or they can serve as carrier for gene delivery [20,21].

However, to our knowledge, the antibacterial activity of such fundamental precursors has not been investigated. So in this paper, we report on the synthesis of two series of quaternary ammonium monomers and discuss the chemical–biological relationships, mainly the bond between molecular structure and biological activity as precursor of bioactive materials.

2. Results and discussion

2.1. Chemistry

Because of the poor solubility of quaternary ammonium compounds in common organic solvents, the strategy to get ammonium compounds is to introduce the quaternary nitrogen as far as possible along the synthesis. Moreover, this minimizes the need of difficult manipulations due to the surfactant nature of the compounds and simplifies many isolation and purification problems [22,23]. Our general synthetic pathway is described in Scheme 1.

The molecules were coded H·*m*·*n* where *m* is the number of carbon atoms in the spacer linking the ammonium head to the acrylic moiety and *n* is the number of carbon atoms in the side hydrocarbon chain (see Scheme 1). The benzylic compounds were coded H·*m*·Bz. For the ethylenic spacer compounds, the starting material was the commercial 2-(dimethylamino)ethyl acrylate on which a bromoalcane is added. On the other hand, the undecylenic spacer compounds need to prepare the corresponding 11-(dimethylamino)undecyl acrylate. To do so, a tertiary amino-alcohol intermediate is first prepared from commercially available 11-bromoundecanol using a nucleophilic substitution with *N*,*N*-dimethylamine stabilized in ethanol. Then, the corresponding polymerizable acrylic tertiary amine is prepared using an esterification reaction in the presence of acryloyl chloride. The reaction is conducted in dry acetonitrile to avoid the precipitation of the tertiary ammonium formed during the esterification reaction. The final polymerizable tertiary amine is finally recovered after a soft basic treatment. The formation of the quaternary ammonium species was performed by reacting the polymerizable amine with different commercial alkyl or benzyl bromide. The Menschutkin reaction was conducted in solvent-free condition, to give the products with good yields and purity.

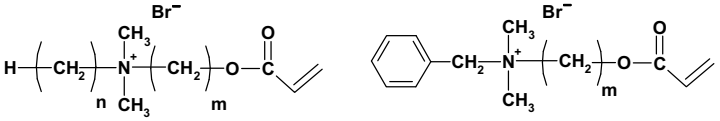
2.2. Surface active properties

2.2.1. Critical micellar concentrations (CMC)

Keeping in mind many other parameters (molecular structure, concentration of the sample, temperature, ionic force), it is generally admitted that the driving force of the micellization phenomenon is mainly governed by the hydrophobicity of the structures [24]. Aggregation of surfactant compounds in water is largely controlled by hydrophobic interaction generated by the non-polar chains of the surfactant. The formation of micelles is a balance between the inherent hydrophobicity of the surfactant and its ability to generate intermolecular interactions. The values of the critical micellar concentrations (CMC) measured for the prepared hydrocarbon polymerizable surfactants are shown in Table 1.

For ionic surfactants, the variation of the CMC vs. the number of carbons (n) of the hydrophobic chain generally follows the empirical Klevens equation: Log (CMC) = $A - Bn$ where A and B are specific values for a homologous series [25]. The A coefficient varies according to the nature of the hydrophilic groups of the surfactant while B, the slope of the curve Log (CMC) vs. n, characterizes the variation of the CMC according to the length of the hydrophobic chains [25]. The B coefficient gives a real indication of the impact on the general hydrophobicity of the studied hydrophobic tail. As shown in Fig. 2, both series of the studied surfactants (the short spacer series with $m = 2$ and the long spacer series with $m = 11$) follow the Klevens relation Log (CMC) = $A - Bn$. Indeed, in both cases, increasing the length of the alkyl chain involves a linear decrease of the logarithm of the measured CMC values. In all cases, for the same alkyl side chain, the surfactant with a long spacer ($m = 11$) connecting the acrylic part to the polar head of the surfmer shows a lower CMC value than the surfactant with a short spacer ($m = 2$). The calculated B coefficients are respectively 0.13 for ethylenic spacer surfmers and 0.20 for undecylenic spacer surfmers. Increasing the spacer enhances the hydrophobic influence of the addition of methylene units and tends to join the values observed in the literature for *n*-alkane hydrocarbon surfactants (about 0.29) having one ionic head [26].

2.2.1.1. Free energy. The micellization phenomenon is spontaneous from the CMC. It is thus characterized by a negative Gibbs micellization free energy (ΔG^0_M). ΔG^0_M is associated with the transfer of a surfactant from the aqueous phase to the micellar pseudophase. The calculation of the micellization free energy, according to the structural parameters of surfactant, is carried out starting from the general equation suggested by Zana [27]. For an ionic surfactant



Cpds	Codes	m	Alkyl or aryl chain	Cpds	Codes	m	Alkyl or aryl chain
1	H.2.Bz	2	$C_6H_5CH_2$	**6**	H.11.Bz	11	$C_6H_5CH_2$
2	H.2.10	2	$C_{10}H_{21}$ (n = 10)	**7**	H.11.10	11	$C_{10}H_{21}$ (n = 10)
3	H.2.12	2	$C_{12}H_{25}$ (n = 12)	**8**	H.11.12	11	$C_{12}H_{25}$ (n = 12)
4	H.2.14	2	$C_{14}H_{29}$ (n = 14)	**9**	H.11.14	11	$C_{14}H_{29}$ (n = 14)
5	H.2.16	2	$C_{16}H_{33}$ (n = 16)	**10**	H.11.16	11	$C_{16}H_{33}$ (n = 16)

Fig. 1. Schematic structures of the investigated surfmers.