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Gemini surfactants from natural amino acids

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ABSTRACT

In this review, we report the most important contributions in the structure, synthesis, physicochemical (surface adsorption, aggregation and phase behaviour) and biological properties (toxicity, antimicrobial activity and biodegradation) of Gemini natural amino acid-based surfactants, and some potential applications, with an emphasis on the use of these surfactants as non-viral delivery system agents. Gemini surfactants derived from basic (Arg, Lys), neutral (Ser, Ala, Sar), acid (Asp) and sulphur containing amino acids (Cys) as polar head groups, and Geminis with amino acids/peptides in the spacer chain are reviewed.

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1. Introduction

Numerous structural modifications to the surfactant structural design have been carried out to increase hydrophobicity in an effort to

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enhance their efficiency. Among them, Gemini or dimeric surfactants with two hydrophilic heads and two hydrophobic groups per molecule separated by a covalently bound spacer chain at the head groups have generated a high interest both from an industrial as well as academic point of view. These compounds were reported for the first time by Bunton et al. [1] but named as 'Gemini' by Menger and Littau in 1991 [2].

The growing interest in these bifunctional active surface agents results from their unusual physicochemical properties. Their interfacial activity and molecular aggregation properties can be modified by adjusting the three structural elements that characterise them (two polar head groups, two aliphatic chains and one spacer) obtaining new surfactants with superior performance compared to the corresponding counterpart single chain surfactants [3,4].

In the last twenty years, a great effort has been made to design and synthesise a large variety of Gemini surfactants changing the ionic and chemical structure of the head group, the type and length of the spacer chain, the effect of the hydrophobic chain length, the points of connectivity of the tails as well as the symmetry of the molecule, [5–15]. There are several reviews concerning the synthesis, structure and properties of Gemini surfactants and in the literature there are plenty of scientific papers and patents of different charged Geminis whose hydrophilic head groups contain dicarboxylates, disulphonates, diphosphates, bis quaternary ammonium, sugars, and amino acid structural functions among others [3,16–32].

The first and most widely conducted investigations have been focused on cationic Geminis with quaternary ammonium head groups and linear hydrocarbon tail groups (also called bisQuats), which are referred to as Cm–Cs–Cm, and where m and s stand for the number of carbon atoms of the alkyl side chain and the methylene spacer, respectively (Fig. 1) [33–39]. They were easy to design andsynthesise [40], and given their peculiar structure were much more efficient (less amount of surfactant needed to achieve the same activity) than a conventional monoQuat surfactant. However, given that they are quaternary ammonium salts, bisQuats are very stable molecules with a poor chemical and biological degradability. This constitutes a risk of toxicity to aquatic organisms, which could make them ecotoxicologically and environmentally unacceptable.

α-Amino acids are the basic structural units of proteins and are linked through peptide bonds. The 20 amino acids that are found within proteins convey a vast array of chemical versatility, and their general formula is represented in Fig. 2. The four different substituents of the asymmetric carbon atom make α-amino acids chiral molecules.

All amino acids found in proteins have this basic structure, differing only in the structure of the R-group of the side chain. These side chains have a widespread range of chemical and structural diversity. On the basis of the ionic nature of R, natural amino acids can be classified into neutral amino acids with a nonionic side chain that can be weakly hydrophilic, hydrophobic or aromatic (i.e. serine, proline, alanine, leucine and phenylalanine), acidic amino acids which are highly polar, and are nearly always negatively charged at physiological pH (i.e. glutamic acid, aspartic acid) and basic amino acids whose side chains are positively charged at physiological pH (i.e. lysine, arginine). Additionally, sulphur-containing amino acids, (i.e. cysteine/cystine) are generally considered to be non-polar and hydrophobic. With the exception of glycine, they are compounds with strong optical activity.

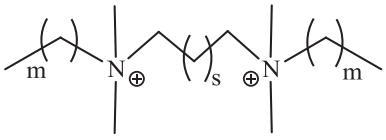

Fig. 1. Schematic structure of bisQuats Gemini surfactants. m stands for the carbon atom number of the alkyl side chain, and s for the number of methylene groups in the spacer chain.

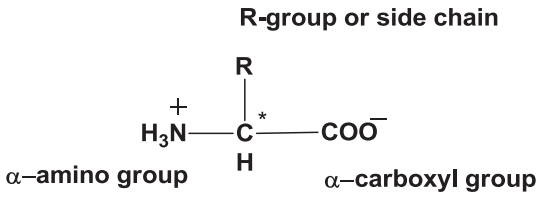

Fig. 2. General formula of α-amino acids. The asymmetric carbon is shown with (*).

The common feature of α-amino acids is the presence of carboxylic acid and amine functionalities, and indeed, most of the reported (bio-) chemical information is focused on reactivity, transformation and derivatization of these groups [41]. The existing literature concerning the use and transformation of amino acids is extremely diverse. In general, however, most studies focus on nutrition, medicine, or the impact on physiological function [42]. Nevertheless, amino acids are also excellent raw materials for the chemical preparation of surfactants. These compounds constitute an important class of natural surface-active bio-molecules of great interest to organic and physical chemists as well as to biologists, with an unpredictable number of basic and industrial applications [43–47].

With the aim to develop biocompatible surfactants with multifunctional properties, our group, in collaboration with others, has synthesised and studied for more than 25 years, a considerable number of new monodisperse amino acid-based surfactants by the combination of amino acids with long aliphatic chains [48]. The introduction of amino acids into the structure of the new surfactant molecules results in remarkable biocompatible properties and a large variety of chemical functionalities, resulting in new surfactants which are chiral, water soluble, non-toxic if orally administered, non-irritating, biodegradable, with a minimal aquatic impact. All these properties guarantee their ultimate commercial development in the food and cosmetic sector and highlight their potential for biochemical applications [49–52].

The amino acids and long aliphatic chains can be combined to generate three main amphiphilic structures (Scheme 1): linear or single chain (a), consisting of an amino acid bearing at least one hydrophobic tail [53–58]; Glycerolipid like structures (b), which can be considered analogues of mono, diglycerides and phospholipids, and consisting of one polar head and one or two hydrophobic moieties linked together through a glycerol skeleton [49, 59–61]; and dimeric or Gemini (c), with two polar heads (*i.e.* two amino acids) and two hydrophobic tails per molecule separated by a covalently bound spacer structure of different ionic character and polarity [62–64].

In the following, we review the most important contributions found in the literature in the structure, synthesis, physicochemical (surface adsorption, aggregation and phase behaviour) and biological (toxicity, antimicrobial activity and biodegradation) properties of amino acid-based Gemini surfactants, and some potential applications therein, with an emphasis on drug and non-viral delivery system agents.

2. Structure and synthesis

2.1. Gemini surfactants with amino acids or peptides as headgroups

One approach to minimise the toxicity of cationic bisQuats surfactants was to design soft Gemini molecules from biocompatible single chain amino acid-based surfactants. These new molecules combine the advantages of Gemini surfactants in terms of efficiency with the biocompatibility of amino acids (biodegradability, and lower toxicity). The first attempt to prepare cationic Gemini surfactants from amino acids was made by Pérez et al. [62] starting from arginine, a basic amino acid, using classical synthetic liquid-phase peptide chemistry. This original work and subsequent studies on