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# Synthesis and properties of a novel bolaamphiphile surfactant derived from proline



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## ABSTRACT

A novel bolaamphiphile surfactant *N,N'*-(octane-1,8-diyl)bis(pyrrolidine-2-carboxamide) (DAOP), was designed and synthesized from proline and 1,8-diaminooctane, as the hydrophilic part and hydrophobic part, respectively. After separation and purification, the structures of the synthesized bola surfactants were verified by IR, MS and <sup>1</sup>H NMR. The pK<sub>a</sub> was measured by a titration experiment, the turbidity was determined using a Shimadzu UV-1750 spectrophotometer, and the critical micelle concentration (CMC) values of the synthesized surfactants in water were obtained using the conductivity and fluorescence probe measurements. The synthesized bolaamphiphile surfactants demonstrate the ability of self-assembly to form vesicles that were confirmed with dynamic light scattering and transmission electron microscopy. The results showed that the novel bolaamphiphile surfactant derived from proline might potentially be an excellent carrier for drug delivery.

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## 1. Introduction

Bolaamphiphiles are a novel type of surfactants with two hydrophilic polar head groups linked *via* a single or multiple hydrophobic alkyl chains, which are drastically different from the conventional single head surfactants [1]. The special structure of bolaamphiphiles allows them arrange into mono-layer membrane (MLM) in aqueous solution to form vesicles that can be applied in drug delivery [2,3]. Compared with the conventional bilayer liposome membrane (BLM) vesicles, MLM vesicles made with bolaamphiphiles are more stable [4]. This is because BLM vesicles may grow by fusion, while fusion is hindered in MLM vesicles due to the energy barrier caused by the difficulty encountered by the polar head groups in the process of crossing the hydrophobic membrane. This energy barrier also reduces the amphiphile exchange between vesicles and biological surfaces. In addition, the MLM vesicles of bolaamphiphiles have higher encapsulation capacity because of the larger inner aqueous core [5], and better controllable release behaviors as a result of the ability to switch from a vesicular structure to nano-ribbons, nanotubes or cylinders

[6]. These advantages have made MLM vesicles of bolaamphiphiles excellent candidates in a number of paramount applications, such as biomimicking, controllable or targeted drug delivery, and imaging. Some research had been indicated that the synthetic bolaamphiphile molecules can form vesicles, which proved their ability of self-assembly, while more bolaamphiphiles inclined to form other structures such as fibers or liquid crystals [4,6]. Due to the highly symmetric structure, it is a challenge for the synthetic bolaamphiphiles to form vesicle when applied as the drug carriers. Recently, some research had reported that it was more easily to form vesicles through the mixture of cholesterol [7] or other type surfactants [3] than that of the single one, herein bolaamphiphiles are promising nonconventional surfactants exploited in mixed surfactant formulations in drug delivery.

The hydrophilic parts of bolaamphiphile play a key role in fabricating functional MLM vesicles. For this reason, various functional groups were chosen as the hydrophilic part, such as fatty acids [8], thiophenes [9], and aza-crown-ethers [10]. Recently, peptidic bolaamphiphiles using amino acids [11,12] as polar group have acquired more popularity. These molecules demonstrate a marked ability for self-organization in bulk solutions to form vesicles by adopting the self-assembly principles of amino acids while maintaining the characteristics of the oligopeptides [13]. This makes the peptidic bolaamphiphiles biocompatible, and the amino and carboxyl groups also endow these amphiphiles pH

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responsiveness. In this regard, the MLM vesicles made with the peptidic bolaamphiphiles are potential carriers for targeted drug delivery [14]. Both hydrophilic and hydrophobic drugs can be loaded in the spherical MLM vesicles [15,16], and drug release may occur in acidic environments as a result of protonation of the amino group that increases the surfactants' solubility and leads to the transformation of vesicle to other structures [17]. Since the pH value in tumor cells is low, the pH regulated drug release is expected to have great potential in cancer treatment.

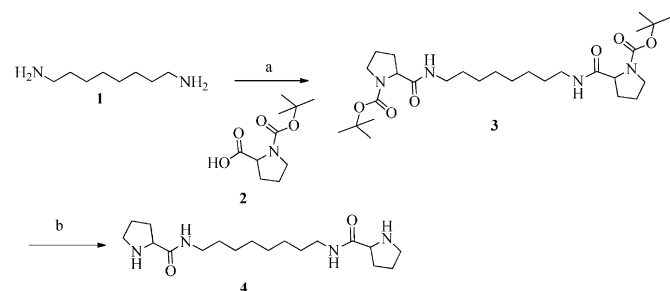
In the present study, a novel peptidic bolaamphiphile, *N,N'*-(octane-1,8-diyl)bis(pyrrrolidine-2-carboxamide) (DAOP), was designed and synthesized from proline and 1,8-diaminooctane, as the hydrophilic part and hydrophobic part, respectively. Proline is one of the twenty essential amino acids, which is critical in the construction of human bone and enamel. The structures of the synthesized bola surfactants were verified by MS, FTIR and <sup>1</sup>HNMR. The pK<sub>a</sub> was measured by the acid–base titration method, the turbidity measurement was carried out using a Shimadzu UV-1750 spectrophotometer at 660 nm, and the critical micelle concentration (CMC) in water was determined by conductivity and fluorescence probe measurements. The vesicles of DAOP could be potential pH sensitive drug carriers.

## 2. Experimental

### 2.1. Synthesis of the proline-based bolaamphiphile

The bolaamphiphile, *N,N'*-(octane-1,8-diyl)bis(pyrrrolidine-2-carboxamide) (DAOP), was synthesized following the procedure in Scheme 1. Firstly, 1,8-diaminooctane (**1**) and Boc-protected proline (**2**) reacted under alkaline conditions in the presence of the catalyst [(Benzotriazol-1-yloxy)tris(dimethylamino)phosphoniumhexafluorophosphate(BOP)] to obtain compound **3**. The compound **4** was prepared by the removing of the protective group (Boc) in HCl [18,19]. The details of the synthesis are given below:

The synthesis of compounds **3**: 1,8-Diaminooctane (0.288 g, 2 mmol) was stirred and dispersed in 10 mL of dry dichloromethane followed by the addition of ethyldiisopropylamine (DIEA, 0.83 mL, 5 mmol), BOP (2.360 g, 5 mmol). The temperature was maintained at 22 °C while Boc-Pro-OH (1.071 g, 5 mmol) was dissolved in 5 mL of dry dichloromethane and added to the solution. The mixture was gradually dissolved under magnetic stirring. After 4 h, the solution was allowed to cool down to room temperature. The solvent was removed at reduced pressure, and 16 mL of ethyl acetate was added. The solvent was extracted with 20 mL of distilled water, 20 mL of saturated sodium bicarbonate and 20 mL of saturated sodium chloride solution. The ethyl acetate solution was dried overnight with anhydrous sodium sulfate. By evaporation under vacuum, yellow oil was obtained (1.64 g, yield: 95.7%).



**Scheme 1.** The synthesis route of DAOP. Condition and reagent: (a) BOP, DIEA, 22 °C, 4 h, 95.7%; (b) HCl, r.t., 2 h, 95.1%.

The synthesis of compounds **4**: The above bolaamphiphile precursor (0.646 g, 1.2 mmol) was stirred and dissolved in about 10 mL of dry ethyl acetate. A white solid precipitated out of solution by bubbling dry hydrogen chloride and isolated by filtration. Precipitation was dissolved in anhydrous methanol and dry hydrogen chloride was bubbled until *N*-Boc protection of amines was removed completely. Yellow oil was obtained after the solution was removed at reduced pressure (0.38 g, yield: 95.1%).

### 2.2. Physicochemical characterization of the DAOP

The pK<sub>a</sub> was measured by the acid–base titration method. The turbidity measurement was carried out using a Shimadzu UV-1750 spectrophotometer at 660 nm. The DAOP vesicles were prepared at different pH from 6.0 to 9.0 in the same DAOP concentration (18 mmol/L) [20,21]. The critical micelle concentration (CMC) of DAOP in water was determined by conductivity and pyrene fluorescence spectroscopy. The pyrene was dissolved in ethanol and about 6 × 10<sup>-4</sup> mmol pyrene was added to the sample tube. Then ethanol was removed under reduced pressure for 4 h and 2 mL of varying concentration surfactant was added to the tube. The mixture was ultrasounded for 3 h and incubated for 24 h and then the fluorescence absorbance was measured. Fluorescence absorbance measurements were taken by a multifunctional microplate reader (Mx3000P, ThermoScientific) using 12 mm path length quartz cuvettes. Excitation was done at 334 nm and emissions were recorded at 372 nm and 385 nm. The slit widths for both excitation and emission were fixed at 0.5 nm. Conductivity measurements were carried out at 25.0 °C using a DDS-11A conductivity meter (REX, Shanghai). In double distilled water, the DAOP vesicles self-assembled with a hydrophobic shell and hydrophilic core. Morphology of DAOP micelles was characterized by transmission electron microscopy (TEM, JEM-100CXII, JEOL, Japan). Particle size distribution was recorded by a Particle Size Analyzer (3000 HAS, Malvern).

## 3. Results and discussion

### 3.1. The characterization of DAOP

The structure of DAOP was characterized by IR, MS and <sup>1</sup>H NMR. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 9.72 (s, 2H), 4.10 (t, 2H, *J* = 7.4 Hz), 3.22 (dd, 2H, *J* = 16.7, 11.3 Hz), 3.19–3.15 (m, 2H), 3.14–3.08 (m, 4H), 2.27 (qd, 3H, *J* = 14.4, 7.4 Hz), 1.88 (td, 5H, *J* = 14.2, 7.1 Hz), 1.78 (dt, 2H, *J* = 20.4, 7.5 Hz), 1.47–1.37 (m, 4H), 1.31–1.20 (m, 10H). IR (KBr, cm<sup>-1</sup>): 3421 (NH<sub>2</sub> and CONH, ν<sub>(N-H)</sub>), 1671 (CONH, ν<sub>(C=O)</sub>), 1632 (NH<sub>2</sub>, δ<sub>(N-H)</sub>), 2923 (CH<sub>2</sub>, ν<sub>s(C-H)</sub>), 2857 (CH<sub>2</sub>, ν<sub>a(C-H)</sub>), 1456 (CH<sub>2</sub>, ρ<sub>(C-H)</sub>), 1055 and 1032 (CH<sub>2</sub>, ν<sub>(C-C)</sub>). The mass spectrum showed a molecular weight of 339.3 as [M+H]<sup>+</sup>, consistent with the predicted 338.3.

### 3.2. Physicochemical properties of DAOP

The value of CMC in water was 0.073 mmol/L, measured by the fluorescence probe method (Fig. 1) at 25 °C, and the conductivity was proved 0.042 mmol/L (Fig. 2). Both results are far below the CMC values of conventional surfactants with comparable chain lengths (the reported CMC is 2.20–2.70 mmol/L for AOT and around 8 mmol/L for SDS at 25 °C [22,23]), suggesting the strong self-assembling ability of the bolaamphiphile. The results of the two methods have a minor difference. The reason may be that the conductivity method was not sufficiently precise due to the lack of a sharp kink. As shown in Fig. 2, the variation of the electrical conductivity with the concentration does not show any clear break point around the CMC. The fluorescence probe method was considered to be more accurate for the fluorescence intensity ratio

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