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Synthesis and antimicrobial characterization of novel L-lysine gemini surfactants pended with reactive groups

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Abstract

A series of novel quaternary ammonium gemini surfactants of L-lysine containing ester group were synthesized with high yield rate. The antibacterial and antifungal activities of these gemini surfactants were evaluated by quantifying the minimal inhibitory concentration (MIC). The results indicated that the quaternary ammonium gemini surfactants exhibited improved activity against a broad spectrum of Gram-positive and Gram-negative bacteria as well as fungi. The pended ester group provides a reactive site for incorporating the surfactant into polymers, thus leading to the polymers with high antimicrobial efficiency.

Keywords: Gemini surfactants; Antimicrobial; Quaternary ammonium groups; MIC

With the increasing public health awareness about the effects of bacteria and microorganisms, developing antibacterial or antimicrobial materials has stimulated substantial research interest. Infection control is of utmost importance in a variety of places, which require a high level of hygiene. A variety of antimicrobial agents, such as iodine, quaternary ammonium (QAS), biguanides, phosphonium salt, fluoroquinolones and the polymers containing these species, have been employed to various circumstances including the disinfection of hospital equipment, pharmaceutical production units and food processing facilities.[1–7] Among these antimicrobial agents, quaternary ammonium salts have been the most widely used ones owing to their excellent cell membrane penetration properties, low toxicity, good environmental stability, non-irritation, low corrosivity and extended residence time and biological activity in comparison with other antimicrobial agents.[8,9] However, the use of QAS in some fields has been limited due to the developed microbial resistance against QAS.[10] Therefore, it is urgent to develop the antibacterial and antifungal agents capable of killing harmful microorganisms with the least development of resistance. Several new types of QAS as antimicrobial agents have been reported in the past.[11–17] Recently, much attention has been paid to gemini surfactants,[13–17] which exhibit higher antibacterial activities than the conventional surfactants.[15–17] Meanwhile, antimicrobial polymers have also attracted considerable research interests due to their non-toxicity and non-irritant properties with the improved and prolonged antimicrobial activities, compared with the ordinary low-molecular-weight antibacterial agents.[3,18–22]

Currently, there are two general approaches employed for the attachment of the antimicrobial agents to polymers. One involves the introduction of functional groups or chains to monomers to create the antimicrobial monomers or macromonomers, followed by their polymerization; another is to link the antibacterial agents directly onto polymers backbones to render the polymer as antimicrobial.[22–25] To date, very few papers have reported that gemini surfactant with broad-spectrum antibacterial activities has been specifically designed and synthesized in an attempt to prepare the polymers with extremely high antimicrobial efficiency.

In this study, a series of novel L-lysine gemini surfactants with high yield were synthesized via an efficient and

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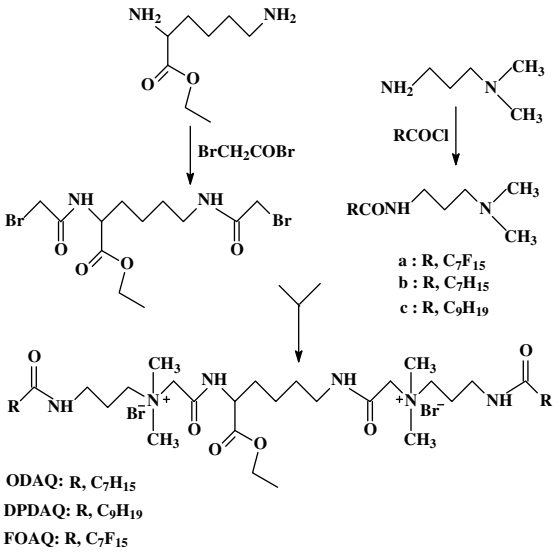
simple approach. The route of synthesis is shown in Scheme 1. *N*,*N*′-Bisbromoacetyl-L-lysine ethyl ester was obtained through the reaction of L-lysine ethyl ester with bromoacetic bromide.[26] Fluorinated or hydrocarbon fatty acid (3-dimethyl amino-propyl) amides were synthesized by the reaction of 1,3-(dimethylamino)-1 -prolylamine with the corresponding chloride.[26] Then L-lysine gemini surfactants were prepared with the two compound analogues described above in the isopropanol refluxing.[26] The antibacterial and antifungal activities of these gemini surfactants were evaluated via determining the minimal inhibitory concentration (MIC) using a commercially available *n*-dodecyl-trimethylammonium bromide (DTAB) as reference.[26] As can be seen from the MIC values presented in Table 1, DPDAQ and FOAQ are more efficient against Gram-positive bacteria, Gram-negative bacteria, yeast and mould than ODAQ. The antibacterial and antifungal activities of as-synthesized gemini surfactants are superior to that of the reference antibacterial agent DTAB. Specifically, the activity against *Staphylococcus aureus* of DPDAQ is 128 times higher than that of DTAB; whereas the corresponding activity against *Escherichia coli* is 64 times higher. It appears that the introduction of a fluorinated chain increased the activity against Candida albicans substantially. In an attempt to further improve the antimicrobial activities of gemini surfactant, a range of novel gemini surfactants pended with functional groups were designed and synthesized. The resulting compounds will be used for synthesizing gemini (macro)monomers or polymers.



Scheme 1. The synthesis route of L-lysine gemini surfactant series.

Table 1
The minimal inhibitory concentration (MIC) results of L-lysine gemini surfactant series and commercial reference (μmol L^{-1})

Samples	*Staphylococcus aureus*[a]	*Escherichia coli*[b]	*Candida albicans*[c]	*Aspergillus niger*[d]
DTAB	250	250	500	250
ODAQ	62.5	62.5	62.5	250
DPDAQ	1.95	3.91	62.5	62.5
FOAQ	7.81	31.25	7.81	62.5

[a] Gram-positive bacteria.
[b] Gram-negative bacteria.
[c] Yeast.
[d] Mould.

In summary, a series of novel quaternary ammonium gemini surfactants containing functional ester group with high yield rate were successfully synthesized. The surfactants possess the broad-spectrum antimicrobial activities; and the synthesis route potentially provides a new strategy for developing the antimicrobial polymers with extremely high activities owing to the polycationic structure. It is well known that polycationic compounds tend to increase the permeability of cell membranes, thus improving the pathogen deactivation.[27,28]

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Supplementary data

Spectral data, synthetic procedures of the compounds and the antimicrobial evaluation in this Letter are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.079.

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26. Experimental details are given in Supplementary data. The selected spectral data are as follows. Data for FOAQ (^{1}H NMR: 300 MHz, TMS $CDCl_3$): δ ppm 1.27: t, $J = 7.2$ Hz, 3H; 1.56: m, 3H; 1.69: m, 1H; 1.88: m, 2H; 2.32: m, 6H; 3.40: s, 3H; 3.42: s, 6H; 3.47: s, 3H; 3.56: m, 4H; 3.64: m, 2H; 3.77: m, 2H; 4.17: m, 2H; 4.41: m, 2H; 4.56: m, 2H; 4.83: m, 1H; 8.52: m, 2H; 8.80: m, 1H; 8.96: m, 1H.
(^{13}C NMR: 300 MHz,TMS $CDCl_3$): δ ppm 14.34: 1C; 23.02: 2C; 23.12: 1C; 27.68: 1C; 29.51: 1C; 37.25: 1C; 38.63: 1C; 52.43: 2C; 52.91: 1C; 53.12: 1C; 53.64: 1C; 61.95: 2C; 63.15: 1C; 63.57: 1C; 64.43: 1C; 64.95: 1C; 105.80–108.42: m, 2C; 108.94–111.59: m, 4C; 112.95–115.93: 4C; 118.89–119.78; 158.87: m, 2C; 162.85: 1C; 162.94: 1C; 171.71: 1C.
(^{19}F NMR: 300 MHz, TMS $CDCl_3$): δ ppm −81.28: 6F; −119.57 to −119.79: 4F; −122.04: 4F; −122.46: 4F; −122.80: 4F; 123.22: 4F; −126.62: 4F.
Ms (positive) theoretical: 1412; observed ((m^{2+}−2Br)/2z): 626.
Data for DPDAQ (^{1}H NMR: 300 MHz, DMSO): δ ppm 0.89: t, $J = 6.3$ Hz, 6H; 1.23: t, $J = 7.2$ Hz, 3H; 1.28: m, 22H; 1.34–1.44: 4H; 1.52: m, 6H; 1.75: m, 2H; 1.88: m, 4H; 2.10: t, $J = 7.5$ Hz, 4H; 3.13: m, 6H; 3.22, s, 12H; 3.50: m, 4H; 4.11: s, 2H; 4.16: m, 2H; 4.21: s, 2H; 4.26: m, 1H; 7.97: m, 2H; 8.65: m, 1H; 9.08: m, 1H.
(^{13}C NMR: 300 MHz, DMSO): δ ppm 14.90: 2C; 14.99: 1C; 23.05: 2C; 23.76: m, 4C; 26.15: 2C; 29.04: 1C; 29.65: 2C; 29.69: 2C; 29.80: 2C; 29.86: 2C; 30.93: 1C; 32.24: 2C; 36.38: 2C; 39.23: 1C; 52.09: 4C; 53.32: 1C; 61.74: 2C; 62.57: 1C; 62.82: 1C; 63.76: 1C; 64.03: 1C; 163.85: 1C; 164.32: 1C; 172.11: 1C; 173.36: 2C.
Ms (positive) theoretical: 928.8; observed ((m−2Br)/2z): 384.3.
Data for ODAQ (^{1}H NMR: 300 MHz, DMSO): δ ppm 0.90: t, $J = 6.3$ Hz, 6H; 1.23: t, $J = 7.2$ Hz, 3H; 1.28–1.40: m, 18H; 1.52: m, 6H; 1.75: m, 2H; 1.88: m, 4H; 2.10: t, $J = 7.2$ Hz, 4H; 3.13: m, 6H; 3.22, s, 12H; 3.50: m, 4H; 4.11: s, 2H; 4.16: m, 2H; 4.20: s, 2H; 4.26: m, 1H; 7.97: m, 2H; 8.64: m, 1H; 9.08: m, 1H.
(^{13}C NMR: 300 MHz, DMSO): δ ppm 14.84: 2C; 14.97: 1C; 22.98: 2C; 23.70: m, 4C; 26.10: 2C; 29.00: 1C; 29.39: 2C; 29.61: 2C; 30.89: 1C; 32.07: 2C; 36.35: 2C; 39.21: 1C; 52.06: 4C; 53.30: 1C; 61.71: 2C; 62.57: 1C; 62.82: 1C; 63.76: 1C; 64.04: 1C; 163.81: 1C; 164.28: 1C; 172.06: 1C; 173.30: 2C.
Ms (positive) theoretical: 872.8; observed ((m−2Br)/2z): 356.3.
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