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Authors: Yugen Zhang and Yuan Yuan

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The Synthesis of Imidazolium Oligomers with Planar and Stereo Cores and Their Antimicrobial Applications

Yuan Yuan,[a] and Yugen Zhang*[a]

[a] Dr. Y. Yuan and Dr. Y. Zhang
Institute of Bioengineering and Nanotechnology,
31 Biopolis Way, The Nanos, Singapore 138669, Singapore.
E-mail: ygzhang@ibn.a-star.edu.sg

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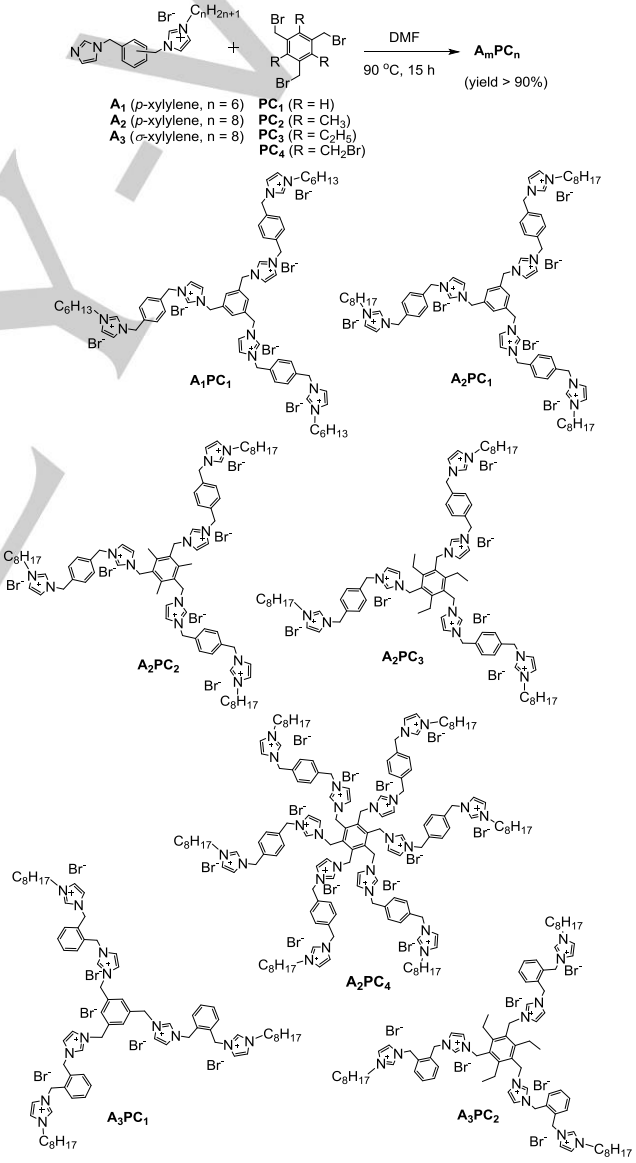
Abstract: A series of imidazolium oligomers with novel planar and stereo core structures were designed and synthesized. These compounds have symmetric structures with different cores, tails and linkers. These novel imidazolium oligomers demonstrated a desirable set of bioactivities against four types of clinically relevant microbes including *E. coli*, *S.aureus*, *P. aeruginosa* and *C. albicans*. The planar oligomers with three di-imidazolium arms and *n*-octyl tails showed good antimicrobial activity and biocompatibility. Oligomers with *ortho*-xylylene linker exhibited higher antimicrobial activity and higher hemolytic ability compared to those oligomers with *para*-xylylene linker. These results shed light on structure-property-relationship of synthetic polymeric antimicrobials.

Imidazolium salt based materials have been widely used in various applications, such as catalysis (precursor of N-heterocyclic carbene ligand),[1] absorbent for CO_2 capture,[2] organo catalyst,[3] ionic liquids (ILs),[4] electrolytes,[5] anticancer and antimicrobial materials.[6] Both monomeric and polymeric imidazolium salts, as well as their derivatives, have been well studied.[1,7] Dimeric, trimeric or tetrameric imidazoliums have also been investigated as ligands for catalysis[1,8] or for the construction of porous metal organic frameworks (MOFs).[9] Dimeric imidazolium showed high antimicrobial activity and low toxicity to mammalian cells.[10-12] Relatively, there are very limited studies on imidazolium oligomers with five to fifteen imidazolium units in their chain structures.[13] In fact, imidazolium oligomers could have potential in various applications as they have definite molecular weight and versatile molecular structure. Recently, a series of linear imidazolium oligomers has been developed as a new generation of antimicrobials and anti-fungal agents which has broad spectrum antimicrobial property, excellent selectivity and no resistance.[13-14] Herein, new structural motifs of imidazolium oligomers with planar and stereo cores were designed and synthesized. These new imidazolium oligomers also exhibit high antimicrobial activity and selectivity.

Infectious diseases and the increasing threat of superbugs have alerted the importance of hygiene and the usage of antibiotics.[15] Currently, small molecular antimicrobial agents, such as triclosan and guanidine derivatives, are extensively used in consumer care products to inhibit microbial growth for preventing infections. However, triclosan and guanidine derivatives have caused many concerns such as drug resistance and toxicity to the environment.[16] Synthetic polymeric materials that act via a membrane-lytic antimicrobial mechanism generally have broad spectrum antimicrobial activities against bacteria, fungi and biofilms, and are capable of preventing drug resistance.[17-18] All previously reported antimicrobial imidazolium oligomers possess linear chain structures.[13-14] The novel imidazolium oligomers with planar and stereo cores would help us to gain more insights into the bacteria killing mechanism of synthetic polymers/oligomers.[19]

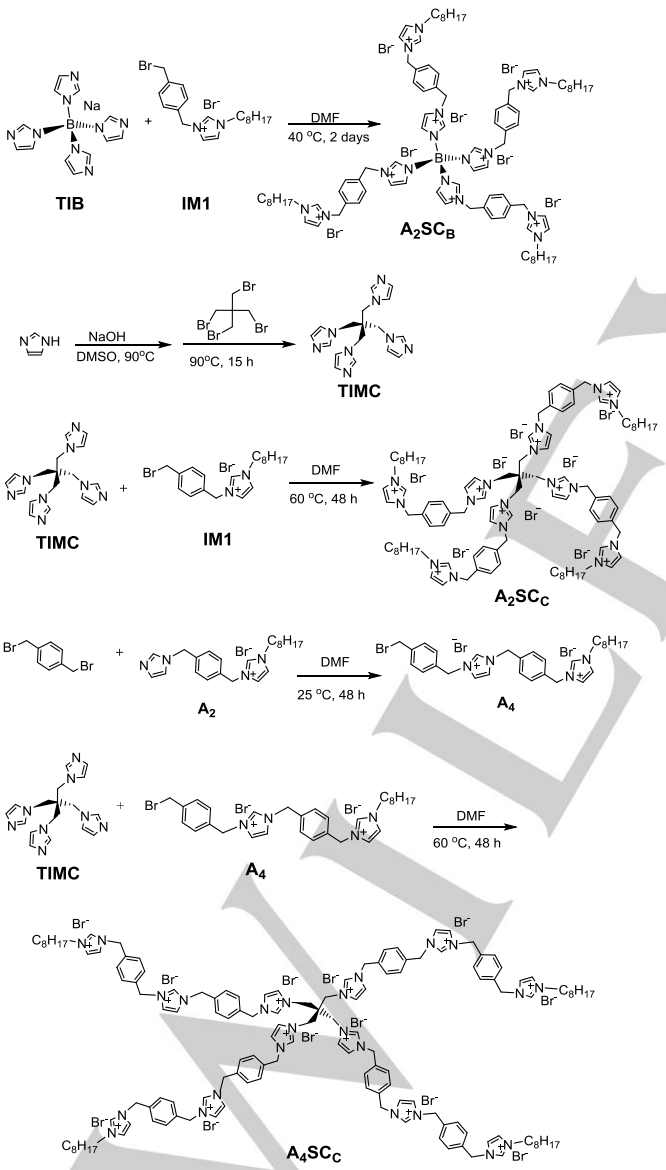


Scheme 1. Imidazolium oligomers with planar core structures.

The new imidazolium oligomers were synthesized by assembling pre-synthesized imidazolium arms with planar or stereo cores, as shown in **Scheme 1** and **2**. For the synthesis of

planar imidazolium oligomers, di-imidazolium arms (A_1 to A_3) were prepared based on a reported method.[20] Di-imidazolium arms were then condensed with a planar core (PC_1 to PC_4) to give planar imidazolium oligomers A_mPC_n. These imidazolium oligomers have similar benzene cores with three or six di-imidazolium arms. The di-imidazolium arms have *o*- or *p*-xylylene linkages and *n*-hexyl or *n*-octyl ending groups.

To synthesize stereo imidazolium oligomers, two types of stereo cores of tetrakisimidazolylborate (**TIB**)[21] and tetra(imidazolylmethyl)carbon **(TIMC)** were prepared. The stereo cores were condensed with imidazolium intermediate (IM1 or $\mathbf{A_4}$) to form final stereo oligomers ($\mathbf{A_2SC_B}$, $\mathbf{A_2SC_C}$ and $\mathbf{A_4SC_C}$) that have a pyramid core of borate or carbon and four di-imidazolium arms ($\mathbf{A_2}$ or $\mathbf{A_4}$). The successful synthesis of these novel structural motifs of imidazolium oligomers would lead to wide potential applications. In this paper, we will focus on their biological application as antimicrobials.



Scheme 2. Imidazolium oligomers with stereo core structures.

These new imidazolium oligomers have different geometric structures compared to previously-reported linear oligomers. Their antimicrobial activities were then evaluated against four different and clinically relevant microbes: *S. aureus*, *E. coli*, *P. aeruginosa*, and *C. albicans*.

The MICs of all 9 oligomers against the four microbes were presented in **Table 1**. All the planar and stereo compounds exhibited antimicrobial activity against the tested microbes. $\mathbf{A_2PC_1}$ showed higher antimicrobial activity than $\mathbf{A_1PC_1}$ due to the more hydrophobic *n*-octyl chain at the terminal end compared to the *n*-hexyl chain. The long aliphatic ending group facilitates stronger interaction between the compound and the cell membrane, therefore enhancing antimicrobial activity.[14,18] The MICs against *E.coli* for [*p*-C_8im] based di-imidazolium salts reported by D'anna et. al [11] and another series of di-imidazolium salts reported by Al-Mohammed et al. [12] are about 25-50 µg/ml, both of which are higher than $\mathbf{A_2PC_{1\text{-}3}}$. It implied that the planar oligomers are more active than di-imidazolium salts. The MICs of $\mathbf{A_3PC_1}$ and $\mathbf{A_3PC_3}$ against *P. aeruginosa* are lower than that of $\mathbf{A_2PC_1}$ and $\mathbf{A_2PC_2}$, respectively. The *ortho*-xylylene linker is probably more suitable for the formation of amphiphilic topography, which facilitates the polymers to bind to the lipid membrane, leading to membrane rupture and eventually cell death. $\mathbf{A_2PC_4}$ showed relatively weak activity against bacteria, which may be due to its low solubility in water and rigid structure As compared to linear imidazolium oligomers, the planar and stereo compounds have bulkier cores and higher positive charge density. The positive charges are confined in the core part and the hydrophobic alkyl chains are located in the outer layer, especially for $\mathbf{A_3PC_x}$ and $\mathbf{A_2PC_4}$. It forms a positively-charged hydrophilic core and neutral hydrophobic shell structure. The result showed that this core-shell type structure is less efficient than the linear structure. Similarly, imidazolium oligomers with stereo core structures are also active against gram-positive and gram-negative bacteria, as well as fungi. $\mathbf{A_2SC_B}$, with a more centralized core, displayed slightly lower antimicrobial activity (against *P. aeruginosa*) as compared to $\mathbf{A_2SC_C}$. As a comparison, we also tested the MICs of conventional antimicrobial agents that are currently used in clinical treatment, such as chlorhexidine for *E. coli*, vancomycin for *S. aureus*, amphotericin B and Fluconzaole for *C. albicans* (SI, STable 1).

Table 1. Antimicrobial (MIC) and hemolytic activities of the synthesized compounds.[a]

	S.A.	*E.C.*	*P.A.*	*C.A.*	HC (10%)[c]
$\mathbf{A_1PC_1}$	32	250	2000	63	>2000
$\mathbf{A_2PC_1}$	4	16	500	63	>2000
$\mathbf{A_2PC_2}$	4	16	1000	63	>2000
$\mathbf{A_2PC_3}$	4	16	250	63	>2000
$\mathbf{A_3PC_1}$	4	8	250	63	500
$\mathbf{A_3PC_3}$	4	16	250	63	250
$\mathbf{A_2PC_4}$	16	63	63	125	32
$\mathbf{A_2SC_B}$	8	16	125	63	500
$\mathbf{A_2SC_C}$	8	16	63	63	125
$\mathbf{A_4SC_C}$	4	63	250	125	500
$\mathbf{IBNC_8}$[b]	4	8	16	16	>2000

[a] Minimum inhibitory concentration (MIC) against 3×10^8 colony forming unit (CFU) mL^{-1} of bacteria 10^6 CFU mL^{-1} of fungus, values are in μgmL^{-1}. [b] Linear imidazolium oligomer with similar components.[11] *S.A.* (*S. aureus*), *E.C.* (*E. coli), P.A.* (*P. aeruginosa*), *C.A.* (*C. albicans*). [c] HC_{10} was taken as oligomer concentration at which the oligomers cause 10% hemolysis.

The morphological changes of bacteria after being treated with these oligomers were observed with SEM. As shown in Figure 1, the cell wall of *E. coli* was disrupted and subsequently dissolved after 3 h exposure to these novel imidazolium oligomers.

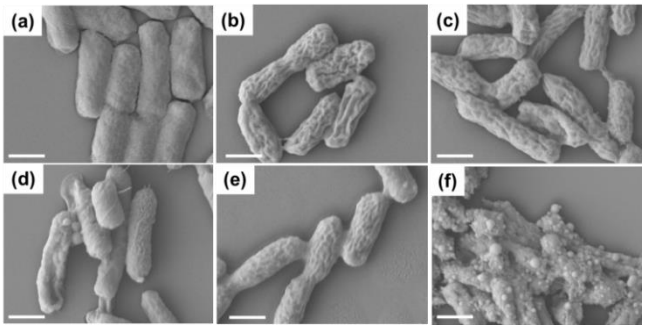


Figure 1. SEM images of *E. coli* treated with planar and stereo compounds (62.5 μg/ml) at 37 °C for 3 h ((a) control, (b) $\mathbf{A_2PC_1}$, (c) $\mathbf{A_2PC_2}$, (d) $\mathbf{A_2PC_3}$, (e) $\mathbf{A_2SC_B}$, (f) $\mathbf{A_2SC_C}$). The cell wall was disrupted after exposure. Bacteria treated with TSB were used as controls. Scale bars represent 1 μm.

The killing kinetics of the planar and stereo compounds were studied against *E coli*. The colony formation units of *E. coli* after being treated with the compounds at 62.5 μg/ml for various periods were shown in **Figure 2**. Although $\mathbf{A_mPC_n}$ and $\mathbf{A_2SC_x}$ have the same MIC against *E. coli*, the speeds that they kill bacteria are different. $\mathbf{A_2SC_B}$ showed the fastest killing speed compared to the other oligomers. Total loss of cell viability was observed within 6 h after exposure. Among the rest of the compounds, $\mathbf{A_2SC_C}$ and $\mathbf{A_2PC_1}$ are more efficient than others. In general, imidazolium oligomers with stereo cores kill bacteria faster than the planar ones but slower than the linear oligomer IBN-C8.[13]

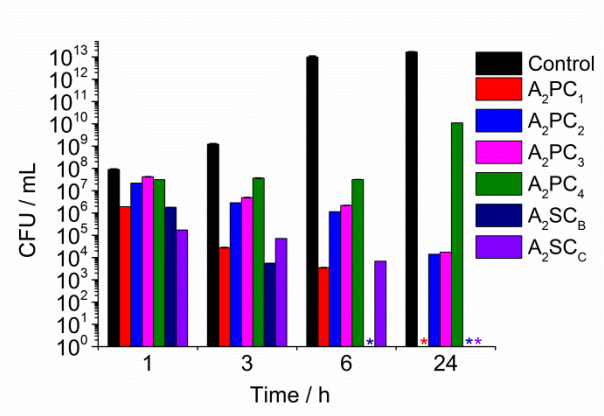


Figure 2. Colony formation units of *E. coli* after being treated with planar and stereo compounds at 62.5 μg/ml for various periods. TSB media without tested compounds was used as a control. * indicates that no colony was observed. The data are expressed as mean ± S.D. of triplicates.

For biomedical applications, the biocompatibility of the compounds with blood is important. Hemolysis assay examines the hemoglobin release by rupturing of red blood cells (RBCs). It is a commonly used method to evaluate the toxicity of antimicrobial compounds.[21] As shown in **Table 1**, the best non-hemolytic properties were observed for $\mathbf{A_{1\text{-}2}PC_{1\text{-}3}}$. No significant hemolysis was observed even at 2000 μg/ml, the highest concentration we tested. They are primarily qualified as active and non-toxic compounds. In contrast, $\mathbf{A_2PC_4}$ caused 10% hemoglobin leakage from RBCs at 32 μg/ml. **It** has 6 arms and 6 octyl ending groups, resulting in the highest hydrophobicity as compared to planar compounds with 3 arms and 3 ending groups. $\mathbf{A_2PC_4}$ exhibited less potency against various microbes but higher toxicity against RBCs, which may be due to its highly centralized core structure. Similarly, $\mathbf{A_3PC_1}$ and $\mathbf{A_3PC_3}$, with *ortho*-xylylene linkers, showed remarkably higher hemolytic activity as compared to oligomers with *para*-xylylene linkers. In the structures of $\mathbf{A_3PC_1}$ and $\mathbf{A_3PC_3}$, with *ortho*-xylylene linkers, all six imidazolium units tend to localize into the core part, whereas for compounds with *para*-xylylene linkers, three outside imidazolium units are stretched out and the positive charges on these molecules are more delocalized. Oligomers with stereo cores ($\mathbf{A_2SC_B}$, $\mathbf{A_2SC_C}$ and $\mathbf{A_4SC_C}$) have relatively high hemolytic activity.

We have designed and synthesized a series of imidazolium oligomers with novel planar and stereo core structures. These compounds have symmetric structures with different cores, tails and linkers. The structural motifs developed here enriched the contents of imidazolium chemistry and have great potential applications. *In vitro* assays demonstrated a desirable set of bioactivities against four types of clinically relevant microbes and shed light on structure-property-relationship of antimicrobials.

Experimental Section

Materials and Methods: For polymer synthesis, all solvents and chemicals were used as obtained from commercial suppliers, unless otherwise indicated. Triton-X was obtained from Aldrich. PBS buffer was used in all experiments. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AV-400 (400 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. ESI-TOF-MS spectra were obtained from a Bruker MicroTOF-Q system. The samples were directly injected into the chamber at 20 $\mu L \cdot min^{-1}$. Typical instrument parameters: capillary voltage, 4 kV; nebulizer, 0.4 bars; dry gas, 2 $L \cdot min^{-1}$ at 120 °C; *m/z* range 40 – 3000.

Minimum Inhibitory Concentration: *Staphylococcus aureus* (ATCC 6538, Gram-positive), *Escherichia coli* (ATCC 8739, Gram-negative), *Pseudomonas aeruginosa* (Gram-negative), and *Candida albicans* (ATCC 10231, fungus) were used as representative microorganisms to challenge the antimicrobial functions of the imidazolium salts. All bacteria and fungus were stored frozen at -80 °C. Bacteria were grown overnight at 37 °C in Tryptic Soy broth (TSB) prior to experiments. Fungus was grown overnight at 22 °C in Yeast Mold (YM) broth. Subsamples of these cultures were grown for a further 3 h and diluted to give an optical density value of 0.07 at 600 nm, corresponding to 3×10^8 CFU mL^{-1} for bacteria and 10^6 CFU mL^{-1} for fungus (McFarland' Standard 1; confirmed by plate counts). The oligomers were dissolved in TSB at a concentration of 4 mg mL^{-1} and the minimal inhibitory concentrations (MICs) were determined by microdilution assay. Typically, 100 μL of microbial solution (containing 3×10^8 cells $mL^{-1}$for bacteria and 10^6 cells mL^{-1} for fungus) was added to 100 μL of TSB or YM broth containing the test imidazolium compounds (normally ranging from 2 μg mL^{-1} to 2 mg mL^{-1} in serial two-fold dilutions)

in each well of the 96-well microtiter plate. The plates were incubated at 37 °C for 24 h with shaking at 300 rpm. For *C. albicans*, the incubation was at room temperature for 48 h. The MICs were taken as the concentration of the antimicrobial oligomer at which no microbial growth was observed with the microplate reader. Broth solution containing microbial cells alone was used as negative control. Experiments were run in quadruplicates.

Time-kill studies: *E. coli* were grown overnight in TSB at 37 ºC. Cells were diluted to 2 ~ 5 x 10^8 CFU/mL, and a 100 µL of this suspension was then added to TSB broth or broth containing 125 ppm of polymer, respectively. Sampling aliquots were withdrawn from cultures at 1, 3, 6 and 24 h after the addition of imidazolium compounds. The aliquots were plated on solid LB plates and incubated at 37 ºC overnight before the colony number was counted. Data from duplicate plate counts were averaged, and the resulting values were plotted on a log scale against time. Experiments were run in triplicates.

Hemolysis: Fresh rat red blood cells (RBCs) were diluted with PBS buffer to give a RBC stock suspension (4 vol% blood cells). 100 µL aliquot of RBC stock was added to a 96-well plate containing 100 µL oligomer stock solutions of various concentrations (obtained from serial 2-fold dilution in PBS). After incubating for 1 h at 37°C, The contents of each well were pipetted into a microcentrifuge tube and then centrifuged at 4000 rpm for 5 min. Hemolytic activity was determined as a function of hemoglobin release by measuring OD576 of 100 mL of the supernatant. A control solution that contained only PBS was used as a reference for 0% hemolysis. 100% hemolysis was measured by adding 0.5% Triton-X to the RBCs. Experiments were run in quadruplicates.

$$Hemolysis(\%) = \frac{OD_{576polymer} - OD_{576blank}}{OD_{576Triton-X100} - OD_{576blank}} \times 100$$

SEM observation: The morphologies of the microbes were observed using a field emission SEM (JEOL JSM-7400F) operated at an accelerating voltage of 5 keV. *E. coli* cells (3×10^8 CFU/ml), with or without imidazolium compounds (62.5 ppm), were grown in TSB for 3 h. The mixtures were collected and centrifuged at 5000 rpm for 6 min. The precipitate was washed with PBS buffer and then fixed with paraformaldehyde (2.5% in PBS) for 3 h, followed by washing with DI water twice. Dehydration of the samples was performed using a series of ethanol/water solution (35%, 50%, 75%, 90%, 95% and 100%). The dehydrated samples were mounted on copper tape. After drying for 2 days, the samples were coated with platinum for imaging with JEOL JSM-7400F (Japan) field emission SEM.

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Keywords: imidazolium oligomer • structural design • antimicrobial

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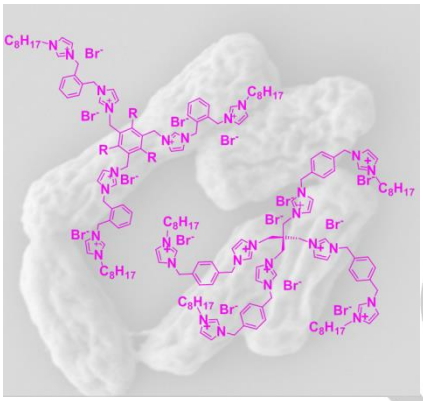

Planar and Stereo Imidazolium Antimicrobials: A series of novel imidazolium oligomers with planar and stereo core were designed and synthesized. They showed good antimicrobial/antifungal activity and biocompatibility. The structure-property relationship study herein shed light on the function-oriented design of synthetic polymeric antimicrobials.