Supporting Information

Experimental:

Instrumentation: ^{1}H and ^{13}C NMR spectra were obtained at 300 MHz and 125 MHz, respectively, with a Bruker DPX-300 NMR spectrometer. The calculations of these urea oligomers were performed at the AM1 level using Spartan '04 for windows from Wavefunction, Inc. Mass spectral data were obtained at the University of Massachusetts Mass Spectrometry Facility which is supported, in part, by the National Science Foundation grant CHE-9974648.

Density-functional theory calculations: The geometries of Figure 4 were each optimized with a single CNCN dihedral angle constraint using the program CPMD 3.4.1.[1] A 12 × 18 × 12 $Å^3$ box, the HCTH functional, and a 70 Ry cutoff were used; otherwise the method was the same as in Ref 2. The curve in Figure 4 is a spline fit to the data points.

Materials: 2,6-Diamino-4-t-butyl-1-(2-t-butoxycarbonylamino ethyl)sulfanylbenzene **3**, was prepared as described in the literature.[3] CDI was purchased from Oakwood Products, Inc. Anhydrous methyl sulfoxide was purchased from EM Science. All other reagents were purchased from Aldrich Chemical Co. and used as received.

General procedure for deprotection of oligomers: A 10 mL round bottom flask was charged with a magnetic stir bar. 25 mg of Boc protected oligomer was added to the flask. The flask was then cooled to 0 ^{o}C and 6 mL of 4M HCl in dioxane was added to the oligomer. The solution was allowed to warm to room temperature and stir overnight. The solvent was evaporated under reduced pressure and the solid was titrated with ether three times and dried under vacuum to yield a yellow solid. ^{1}H NMRwas used to characterize all samples confirming removal of the Boc signals and retention of the other expected signals.

Antimicrobial Testing: All assays followed a modified NCCLS procedure for cationic agents.[4-6] The compounds were dissolved in water to make a stock solution. The stock solution was then diluted into 96-well plates and diluted with Meuller Hinton (MH) medium to a constant volume. Cells were taken from stock glycerol solutions and diluted into MH medium. The cultures were grown for 3 hours, OD_{600} was measured and then the cells were diluted to 0.001 OD_{600}. The diluted cell solutions were then added to the 96-well plate and incubated at 37°C for 6 hours. MIC_{50} was determined by measuring cell growth at OD_{600} after 6 hours. MIC_{50} is a 50 percent reduction in cell count compared to the control sample in the absence of antimicrobial agent. Figure si 1 shows the typical antibacterial data.

Hemolysis Assay: Hemolysis experiments were performed by incubating a 0.35% suspension of fresh human erythrocytes (RBCs) in 10 mM Tris buffer containing 150 mM NaCl at pH 7.0 with varying amounts of polymer. Hemolysis samples were prepared by combining 80 μL of the washed RBC suspension and 20 μL total of buffer and polymer solution in 96-well plates. After incubation for 30 minutes at 37°C, the suspensions were centrifuged at 3000 rpm for 5 minutes. An aliquiot of the supernatant was diluted with buffer and OD_{414} of the solution (due to released hemoglobin) was measured. Complete hemolysis was measured by adding 1% Triton X-100 to the RBC's and measuring OD_{414}. Non-linear exponential curve-fitting plots of OD_{414} vs. polymer concentration resulted in HC_{50}, the hemolytic dose required to lyse 50% of the RBCs.

Synthesis: 324 mg (2 mmol) of CDI was dissolved in 40 mL dry DMSO solution. 2.0 g (5.9 mmol) of 2,6-Diamino-4-t-butyl-1-(2-t-butoxycarbonylaminoethyl)sulfanyl-benzene was added. The resulting mixture was heated at 110 °C for 24 hours. After the reaction mixture was cooled to room temperature, 200 mL ethyl acetate was added. The mixtures were washed with saturated potassium carbonate solution and sodium chloride solution. The organic layer was evaporated to dryness and purified by flash chromatography. The eluent is 200:10:1 methylene chloride / ethyl acetate / mathanol. The dimer, trimer and tetramer were obtained in 20%, 10%, 30% yield respectively. Another 10% portion which can not separated by column chromatography was considered to be the mixture of pentamer, hexamer, heptamer and octamer based on the high resolution MALDI-Mass Sperctra.

Dimer: ^{1}H-NMR (300 MHz, CDCl3): δ = 8.28 (br, 2H), 7.56 (s, 2H), 6.52 (s, 2H), 5.15 (br, 2H), 4.40 (br, 4H), 3.20 (br, 4H), 2.70 (br, 4H), 1.40 (s, 18H), 1.28 (s, 18H). ^{13}C-NMR (125 MHz, CDCl3): δ = 156.20, 154.29, 153.14, 149.11, 141.33, 109.19, 107.33, 103.76, 79.54, 40.45, 35.35, 34.91, 31.09, 30.83, 28.38. High resolution FAB-mass, m/z: calcd: 704.40; found: 704.40 ($M+H^{+}$).

Trimer: ^{1}H-NMR (300 MHz, CDCl3): δ = 8.38 (br, 4H), 7.76 (s, 2H), 7.53 (s, 2H), 6.51 (s, 2H), 5.35 (br, 2H), 5.15 (br, 1H), 4.42(br, 4H), 3.21 (br, 6H), 2.70 (br, 6H), 1.40 (s, 27H), 1.33 (s, 9H). 1.26 (s,18H). ^{13}C- NMR (125 MHz, CDCl3): δ = 156.75, 156.27, 154.06, 153.70, 153.46, 149.11, 141.38, 140.76, 114.86, 109.35, 107.25, 104.03, 79.80, 79.50, 40.77, 40.50, 37.54, 35.22, 34.84, 31.15, 31.06, 30.80, 30.74, 28.40. High resolution FAB-mass, m/z: calcd: 1069.6; found: 1069.4 ($M+H^{+}$).

Tetramer: ^{1}H-NMR (300 MHz, CDCl3): δ = 8.40 (br, 6H), 7.80 (br, 4H), 7.53 (s, 2H), 6.52 (s, 2H), 5.24 (br, 4H), 4.42(br, 4H), 3.22 (br, 8H), 2.70 (br, 8H), 1.40 (s, 36H), 1.32 (s, 18H). 1.23 (s,18H). ^{13}C-NMR (125 MHz, CDCl3): δ = 156.32, 154.13, 153.51, 149.12, 140.87, 114.75, 79.83, 79.60, 40.79, 40.53, 35.24, 34.87, 31.17, 31.09, 30.87, 28.45, 28.41. High resolution MALDI-Mass, m/z: calcd: 1457.7; found: 1457.5($M+Na^{+}$).

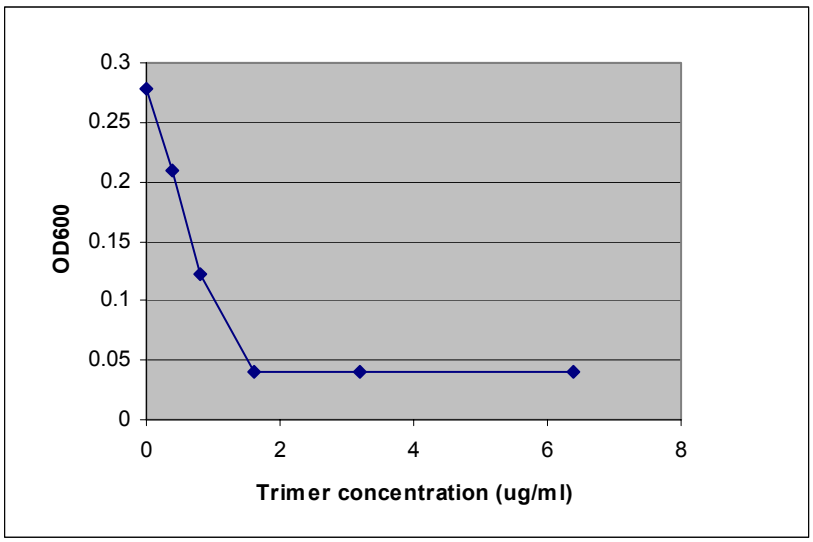

Figure S1. Representative antibacterial experiment data of urea trimer, **5,** against *E. Coli.*

NMR titration: Trimer, **5**, was dissolved in $CDCl_3$ and titrated with DMSO-d_6 at 10 % increments from 0% to 100% DMSO. The chemical shifts for the urea NHs and Boc NHs were compared. The Boc NHs protons are unlikely to be involved in any intramolecular hydrogen bonding and thus are an internal control. The change in ppm was determined to be 0.47 and 1.65 ppm for the urea NHs and Boc NHs respectively.

References:

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3 G. N. Tew, D. Liu, B. Chen, R. J. Doerksen, J. Kaplan, P. Carroll, M. L. Klein, W. F. DeGrado, *Proc. Nat. Acad. Sci. U.S.A.,* 2002, **99**, 5110-5114.
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