Crescent Oligoamides as Hosts: Conformation-Defined Binding Specificity

Kazuhiro Yamato, a Lihua Yuan, a,d Wen Feng, a,d Amber J. Helsel, a Adam R. Sanford, a Yunfeng Zhang, b Jin Zhu, b Jingen Deng, b Xiao Cheng Zeng, c and Bing Gong*a

a Department of Chemistry, Natural Sciences Complex, University at Buffalo, The State University of New York, Buffalo, New York 14260, USA

b Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041

c Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska 68588, USA

d Current address: College of Chemistry and Institute of Nuclear Science and Technology, Sichuan University, Chengdu, 610064, Sichuan, China

Supporting Information
**General Methods.** Chemicals were purchased from Aldrich and Fisher (Acros), and were used as received unless otherwise indicated. CH$_2$Cl$_2$ was dried over CaH$_2$. Unless specified, all solvents were removed with a rotary vacuum evaporator. All reactions were performed under argon in the absence of light. Analytical thin layer chromatography (TLC) was conducted on Analtech Uniplate silica gel plates with detection by UV light.

NMR analyses were carried out on Varian INOVA 500, and Varian INOVA 400 spectrometer at 20 °C (unless otherwise noted). Tetramethylsilane (TMS) or deuterated solvent DMSO-d$_6$ was used as the internal standard for $^1$H NMR. Chemical shifts are reported in ppm values downfield from tetramethylsilane and $J$ values are reported in Hz. MALDI experiments were performed using a Bruker Biflex IV matrix assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometer with a matrix of 9-nitroanthracene or dithranol. Mass spectra were acquired in positive reflector mode with an acceleration voltage of 19 kV. External mass calibration was performed using a standard PEG-2000 mixture. Spectra were obtained by setting the laser power close to the threshold of ionization and generally 300 pulses were acquired and averaged. Solvents were purified and dried according to standard procedures.

**I. Synthesis of Oligomers 5b and 5c**

Oligomers **5b** and **5c** were prepared based on similar procedures we reported previously.$^{1,2}$

**Hexamer 5b.** $^1$H NMR (400 MHz, 10% DMF-$d_7$-CDCl$_3$) 0.68-0.76 (m, 15H), 1.08-1.38 (br, 90H), 1.72-1.82 (m, 8H), 1.83-1.89 (m, 2H), 3.79 (s, 6H), 3.82-4.00 (m, 22H), 4.09 (s, 3H), 6.27 (s, 1H), 6.30-6.48 (s, 4H), 8.49-8.55 (m, 1H), 8.68 (s, 1H), 9.09 (s, 1H), 9.21 (s, 2H), 9.23 (s, 1H), 9.66 (s, 1H), 9.81 (s, 1H), 9.84 (s, 1H), 9.86 (s, 1H), 10.33 (s, 1H). $^{13}$C NMR(75 MHz, 10% DMF-$d_7$-CDCl$_3$) 13.72, 16.34, 21.23, 22.18, 22.29, 24.49, 25.34, 25.51, 27.01, 28.55, 29.60, 29.88, 30.16, 30.44, 30.72, 31.00, 32.33, 34.40, 34.69, 34.97, 35.25, 35.52, 35.80, 36.07, 38.33, 55.51, 56.11, 57.14, 67.43, 68.73, 72.35, 72.40,
94.90, 96.99, 109.29, 113.34, 119.44, 120.65, 121.51, 122.14, 123.38, 127.42, 127.52, 127.76, 128.80, 129.49, 129.61, 132.05, 147.69, 151.27, 153.53, 153.72, 156.35, 159.58.

MALDI TOF MS calcd for C_{107}H_{162}N_{6}O_{18}Na ([M+Na]^+) 1842.2. Found 1842.3.

**Hexamers 5c.** $^1$H NMR (400 MHz, 40% DMSO-$d_6$/CDCl$_3$) 0.88-0.96 (m, 12H), 1.09 (d, $J = 6.7$ Hz, 1H), 1.10 (d, $J = 7.0$ Hz, 1H), 1.18-1.36 (m, 60H), 1.38-1.46 (m, 6H), 1.50-1.62 (m, 8H), 1.82-1.88 (m, 2H), 1.92-1.99 (m, 4H), 2.16-2.24 (m, 2H), 4.01 (s, 3H), 4.06 (d, $J = 6.6$ Hz, 2H), 4.12 (s, 9H), 4.15 (s, 3H), 4.21 (d, $J = 6.7$ Hz, 2H), 4.22-4.29 (m, 8H), 6.25 (s, 1H), 6.43 (s, 3H), 6.78-6.98 (m, 2H), 6.82 (s, 1H), 6.87 (s, 1H), 6.94-7.08 (m, 2H), 7.16-7.20 (m, 1H), 7.36-7.42 (m, 1H), 8.59 (d, $J = 8.5$ Hz, 1H), 8.75 (s, 1H), 9.03 (s, 1H), 9.29 (s, 1H), 9.30 (s, 1H), 9.31 (s, 1H), 9.65 (s, 1H), 10.19 (s, 1H), 10.21 (s, 2H), 10.61 (s, 1H). MALDI TOF MS calcd for C$_{103}$H$_{156}$N$_{9}$O$_{18}$ ([M+G]$^+$) 1809.2. Found 1808.8.


Figure S1. $^1$H NMR spectra of 6mer 5b in 10% DMF$^d$-CDCl$_3$. 
**Figure S2.** $^{13}$C NMR spectra of 5b in 10% DMF$_{d7}$-CDCl$_3$. 
Figure S3. $^1$H NMR spectrum of 5c in 40% DMSO-$d_6$-CDCl$_3$. 
Figure S4. Normal phase HPLC trace of 5c (0.2% CH$_3$OH in CH$_2$Cl$_2$).

Figure S5. MALDI TOF MS spectrum of 5c.
II. MALDI Spectra

The matrix solution of 9-nitroanthracene (20mM, CHCl₃) was pre-spotted (2uL) onto the steel sample target. Host-guest mixtures (1 uL, 1-2 mM, 10% MeOH, 90% CHCl₃) were directly spotted onto the sample well and drawn back into the capillary tube and spotted again to insure an even matrix-sample mixture. The matrix-sample solution was air-dried on the target at ambient temperature.

1. Complexes of Pentamer 2 with Guanidinium and Octylguanidinium Ions

The synthesis of 2 and its dinitro trimer intermediate were described previously by us. The synthesis of 2 and its dinitro trimer intermediate were described previously by us.³

![Figure S6. MALDI spectrum of 2 (2 mM, in 10% methanol in chloroform) in the presence of one equivalent of G•TPB and OG•TPB.](image)
2. Complexes of oligomers 3a, 4a, and 5a

The synthesis of these oligomers was described before by us.\(^1\)

**Figure S7.** MALDI spectrum of tetramer 3a with (a) 1 equiv. guanidinium tetraphenyborate, and (b) 1 equiv. octylguanidinium tetraphenylborate.

**Figure S8.** MALDI spectrum of pentamer 4a with (a) 1 equiv. guanidinium tetraphenyborate and (b) 1 equiv. octylguanidinium tetraphenylborate.
Figure S9. The MALDI spectra of hexamer 5a with (a) 1 equiv. guanidinium tetraphenyborate and, (b) 1 equiv. octylguanidinium tetraphenylborate.

Figure S10. The MALDI spectrum of hexamer 5a (2 mM, in 10% methanol in chloroform) with ten equivalents of G•TPB and one equivalent of OG•TPB.

Figure S11. MALDI spectra of 5a in the presence of one equivalent of octylguanidinium tetraphenylborate and, (a) one equivalent of each of KCl, NaCl, LiCl, CsCl, NH₄Cl, and NMe₄Cl; (b) five equivalents of each of CsCl, RbCl, KCl, NaCl, LiCl, NH₄Cl, and NMe₄Cl.
Figure S12. The MALDI spectrum of hexamer 5b in the presence of one equiv. guanidinium tetraphenyborate and one equiv. octylguanidinium tetraphenylborate.

II. NOESY Spectrum

Partial NOESY spectrum of complex 5a•OG

Figure S13. NOESY spectrum of 5a (1.2 mM) and OG•TPB (1.2 mM) (500 MHz, in 85%CDCl3/15%acetone-d6(v/v), 0°C, mix time=0.5s).

III. Structures Optimized by *Ab initio* Computations

The *ab initio* density-functional calculation was carried out using the Gaussian 03 package.\(^1\) The structures were optimized by using the B3LYP/6-311G(d) level of theory and basis set.

Reference 1:

Figure S14. Conformation of oligomer 2 (all side chain R = CH₃) optimized by *ab initio* computation shows a backbone significantly deviated from planarity.
Figure S15. (a) Conformation of complex 2•OG (all side chain R = CH₃) optimized by *ab initio* computation reveals an overall planar backbone for 2. (b) The conformation of the OG ion in complex 2•OG.
Figure S16. Conformation of complex 5a (all side chain R = CH₃) optimized by ab initio computation reveals that the residue bearing the end methyl group is twisted out of co-planarity, leading to a short depressed portion out of the backbone.
Figure S17. (a) Conformation of complex 5a•OG (all side chain R = CH₃) optimized by ab initio computation reveals minimum disturbance on the backbone of 5a as compared to that of free 5a. (b) The conformation of the OG ion in complex 5a•OG reveals that all the atoms of the guanidinium moiety and the α-carbon are coplanary.
**Figure S18.** Conformation of complex 5b (all side chain R = CH$_3$) optimized by *ab initio* computation reveals an overall flat backbone.
Figure S19. (a) Conformation of complex 5b•OG (all side chain R = CH₃) optimized by *ab initio* computation reveals that the backbone of 5b has become more twisted as compared to that of free 5b. (b) The conformation of the OG ion in complex 5b•OG shows the guanidinium moiety is twisted and nonplanar.
IV. Determination of Binding Constants ($K_a$)

Binding constants $K_a$ in CHCl$_3$ were measured by extraction method developed by Cram and coworkers.$^2$ Guanidium tetraphenyl borate (GTPB) or ethylguanidium tetraphenyl borate (EGTPB) was used as guest molecule. To determine $K_a$ by extraction, we assume that (a) host (oligoamide foldamer) forms only 1:1 complex with guest, (b) host forms tight ion pair complex in CHCl$_3$, (c) host is not soluble in H$_2$O.

$K_a$ can be measured by following equations.

$$
H_{org} + GTPB_{org} \rightleftharpoons K_a \ H-GTPB_{org} \quad (1)
$$

$$
K_a = \frac{[H-GTPB_{org}]}{[H_{org}][GTPB_{org}]} \quad (2)
$$

$$
H_{org} + G^+_{aq} + TPB^-_{aq} \rightleftharpoons K_e \ H-GTPB_{org} \quad (3)
$$

$$
K_e = \frac{[H-GTPB_{org}]}{[H_{org}][G^+_{aq}][TPB^-_{aq}]} \quad (4)
$$

$$
G^+_{aq} + TPB^-_{aq} \rightleftharpoons K_d \ GTPB_{org} \quad (5)
$$

$$
K_d = \frac{[GTPB_{org}]}{[G^+_{aq}][TPB^-_{aq}]} \quad (6)
$$

$$
K_a = \frac{K_e}{K_d} \quad (7)
$$

**Measurement of distribution constant $K_d$**

Guanidium tetraphenylborate (G•TPB): An aqueous solution of GTPB (1 mM, 100 mL) was vigorously stirred with water saturated CHCl$_3$ (1000 ml) for 10 min. Organic phase was separated and evaporated in vacuo. After drying over under high vacuum, weight of extracted GTPB was measured. $K_d$ (GTPB) = 6.21 M$^{-2}$

Ethylguanidium tetraphenylborate (EtG•TPB): An aqueous solution of EGTPB (0.1 mM, 2 ml) and water saturated CHCl$_3$ (1 ml) were placed in centrifuge tube. Tube was vortexed for 30 s and centrifuged for 5 m. Concentration of EGTPB was determined by UV spectrum. $K_d$ (EGTPB) = 2.17×10$^3$ M$^{-2}$

**Measurement of extraction constant $K_e$**

A water saturated CHCl$_3$ solution of oligomer was placed in 15 mL centrifuge tube, then an aqueous solution of guest was added slowly. The tube was vortexed for 30 s and centrifuged for 5 min. Concentration of tetraphenylborate after extraction ([TPB$^-_{aq}$]) was
determined based on $A_{273}$, which changes linearly under given condition (Figure 1). Concentration of other spices was determined by following:

$$[G_{aq}^+]_f = [TPB_{aq}^-]_f \quad (8)$$

$$[H-\text{GTPB}_{org}]_f = ([G_{aq}^+]_0 - [G_{aq}^+]_f)V_{aq}/V_{org} \quad (9)$$

$$[H_{org}]_f = [H_{org}]_0 - [H-\text{GTPB}_{org}]_f \quad (10)$$

where $[H_{org}]_0$ and $[G_{aq}^+]_0$ are initial concentration of host and guest, $V_{aq}$ and $V_{org}$ are volume of aqueous and organic solution. All experimental parameters are summarized in Tables 1-2.

**Figure S20.** UV spectra of GTPB in H$_2$O with various concentration (0-1 mM). inset: plot of $A_{273}$ versus concentration.
Table 1. Extraction profile of Guanidium Tetraphenylborate (GTB) and 6.

<table>
<thead>
<tr>
<th>[G\textsubscript{aq}]\textsubscript{0}</th>
<th>V\textsubscript{aq}</th>
<th>[H\textsubscript{org}]\textsubscript{0}</th>
<th>V\textsubscript{org}</th>
<th>Molar ratio of H and G</th>
<th>K\textsubscript{e}</th>
<th>K\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>mM</td>
<td>ml</td>
<td>mM</td>
<td>ml</td>
<td></td>
<td>M\textsuperscript{2}</td>
<td>M\textsuperscript{-1}</td>
</tr>
<tr>
<td>0.10</td>
<td>5</td>
<td>0.10</td>
<td>3</td>
<td>0.6</td>
<td>1.10\times10\textsuperscript{9}</td>
<td>1.77\times10\textsuperscript{8}</td>
</tr>
<tr>
<td>0.10</td>
<td>5</td>
<td>0.10</td>
<td>4</td>
<td>0.8</td>
<td>1.37\times10\textsuperscript{9}</td>
<td>2.20\times10\textsuperscript{8}</td>
</tr>
<tr>
<td>0.20</td>
<td>5</td>
<td>0.20</td>
<td>3</td>
<td>0.6</td>
<td>6.85\times10\textsuperscript{8}</td>
<td>1.10\times10\textsuperscript{8}</td>
</tr>
<tr>
<td>0.50</td>
<td>2</td>
<td>0.50</td>
<td>1</td>
<td>0.5</td>
<td>7.71\times10\textsuperscript{8}</td>
<td>1.24\times10\textsuperscript{8}</td>
</tr>
<tr>
<td>0.50</td>
<td>2</td>
<td>0.50</td>
<td>1.5</td>
<td>0.75</td>
<td>2.05\times10\textsuperscript{8}</td>
<td>3.31\times10\textsuperscript{8}</td>
</tr>
</tbody>
</table>

K\textsubscript{a} (average) 1.33±0.78\times10\textsuperscript{8} M\textsuperscript{-1}

Table 2. Extraction profile of Ethylguanidium Tetraphenylborate (EGTB) and 6.

<table>
<thead>
<tr>
<th>[G\textsubscript{aq}]\textsubscript{0}</th>
<th>V\textsubscript{aq}</th>
<th>[H\textsubscript{org}]\textsubscript{0}</th>
<th>V\textsubscript{org}</th>
<th>Molar ratio of H and G</th>
<th>K\textsubscript{e}</th>
<th>K\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>mM</td>
<td>ml</td>
<td>mM</td>
<td>ml</td>
<td></td>
<td>M\textsuperscript{2}</td>
<td>M\textsuperscript{-1}</td>
</tr>
<tr>
<td>0.05</td>
<td>2.5</td>
<td>0.05</td>
<td>2</td>
<td>0.8</td>
<td>7.79\times10\textsuperscript{9}</td>
<td>3.59\times10\textsuperscript{6}</td>
</tr>
<tr>
<td>0.10</td>
<td>2.5</td>
<td>0.10</td>
<td>2</td>
<td>0.8</td>
<td>3.86\times10\textsuperscript{9}</td>
<td>1.78\times10\textsuperscript{6}</td>
</tr>
<tr>
<td>0.15</td>
<td>3</td>
<td>0.15</td>
<td>2</td>
<td>0.67</td>
<td>7.08\times10\textsuperscript{10}</td>
<td>3.27\times10\textsuperscript{7}</td>
</tr>
</tbody>
</table>

K\textsubscript{a} (average) 1.27±1.73\times10\textsuperscript{7} M\textsuperscript{-1}