Resorcinarene-based cavitands with chiral amino acid substituents for chiral amine recognition

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Characterization of AME, AMNa, and AMA

The structure of AME

1. $^1$H NMR structure of AME in $d_6$-acetone.

2. 2D COSY of AME in $d_6$-acetone.
3. $^{13}$C NMR of AME in $d_6$-acetone.

4. $^1$H NMR spectrum of AMNa in D$_2$O at 60 °C.
5. 2D COSY of AMNa in D$_2$O.

6. $^1$H NMR spectrum of AMA in d$_6$-DMSO at 80 °C.
7. 2D COSY of AMA in $d_6$-DMSO.

8. Particle size comparison between AME, AMNa, and AMA.

Size Distribution by Intensity
Characterization of GUE, GUNa, and GUA

The structure of GUE

1 $^1$H NMR structure of GUE in $d_6$-acetone.

2D COSY of GUE in $d_6$-acetone
3. $^{13}$C NMR of GUE in $d_6$-acetone.

4. $^1$H NMR of GUBNa in D$_2$O.

5. 2D COSY of GUNa in D$_2$O.
6. FTICR-MS of GUNa (M = GUNa).

M = GUNa;
[M+8H2O-2Na]2- = 1052.02

(calculated: 1052.07); [M+8H2O-Na-H]2- = 1063.06; [M+8H2O-3Na+H]2- = 1040.97;
[M+8H2O-4Na+2H]2- = 1029.97; [M+8H2O-3Na-1Arm+H]2- = 1040.97; [M+8H2O-2Na-1Arm]2- = 921.38; [M+8H2O-Na-1Arm-H]2- = 932.93; [M+8H2O-1Arm-2H]2- = 943.95;
[M+8H2O-3Na-1Arm+H]2- = 910.38; [M+8H2O-3Na]3- = 693.68; [M+8H2O-4Na+H]3- = 1686.22;

7. 1H NMR of GUA in d6-acetone.
8. 2D COSY of GUA in $d_6$-acetone.

9. FTICR-MS of GUA (M=GUA).
10. Particle size comparison between GUE, GUNa, and GUA.

Size Distribution by Intensity

- Red: GUE
- Green: GUNa
- Blue: GUA
Characterization of AUE, AUNa, and AUA.

The structure of AUA

1. $^1$H NMR of AUE in $d_6$-acetone.

2. 2D COSY of AUE in $d_6$-acetone.
3. $^{13}$C NMR of AUE in $d_6$-acetone.

4. $^1$H NMR of AUNa in D$_2$O.

5. 2D COSY AUNa in D$_2$O.
6. FTICR-MS of AUNa (M = AUNa).

\[ [\text{M}+8\text{H}_2\text{O}-\text{2Na-H}]^{3-} = 719.67 \quad (\text{Calculated: 719.77}); \]
\[ [\text{M}+8\text{H}_2\text{O}-\text{Na-2H}]^{3-} = 727.01; \]
\[ [\text{M}+8\text{H}_2\text{O}-\text{3H}]^{3-} = 743.39; [\text{M}+8\text{H}_2\text{O}-\text{3Na}]^{3-} = 712.37; [\text{M}+8\text{H}_2\text{O}-\text{3Na}]^{3-} = 712.37; \]
\[ [\text{M}+8\text{H}_2\text{O}-\text{4Na}]^{4+} = 528.44; [\text{M}+8\text{H}_2\text{O}-\text{3Na-H}]^{4+} = 533.94; [\text{M}+8\text{H}_2\text{O}-\text{2Na-2H}]^{4+} = 539.44; \]
\[ [\text{M}+8\text{H}_2\text{O}-\text{1Na-3H}]^{4+} = 544.93; [\text{M}+8\text{H}_2\text{O}-\text{4H}]^{4+} = 550.70; \]
\[ [\text{M}+8\text{H}_2\text{O}-\text{2Na}]^{2-} = 1080.23; [\text{M}+8\text{H}_2\text{O}-\text{Na-H}]^{2-} = 1091.18; [\text{M}+8\text{H}_2\text{O}-\text{2H}]^{2-} = 1102.28; \]
\[ [\text{M}+8\text{H}_2\text{O}+\text{Na-3H}]^{2-} = 113.27; [\text{M}+8\text{H}_2\text{O}-\text{2Na-1Arm}]^{2-} = 942.52; [\text{M}+8\text{H}_2\text{O}-\text{Na-1Arm-H}]^{2-} = 953.68; [\text{M}+8\text{H}_2\text{O}-\text{2Na-2Arm}]^{2-} = 804.90; [\text{M}+8\text{H}_2\text{O}-\text{Na-2Arm-H}]^{2-} = 815.89; \text{these peaks around 627.91 are the -3 peaks of -2 peaks around 942.52.} \]

7. $^1$H NMR of AUA in d$_6$-acetone.

8. 2D COSY of AUA in d$_6$-acetone.
9. FTICR-MS of AUA (M = AUA+8H2O).


10. Particle size comparison between AUE, AUNa, and AUA.
Various temperatures $^1$H NMR study of AMNa in D$_2$O.
Various temperatures $^1$H NMR study of AMA in $d_6$-DMSO.
Equilibrium Constant Calculations

To calculate equilibrium constants, we used a similar method to that previously published (J. S. Gardner, M. Conda-Sheridan, D. N. Smith, R. G. Harrison, J. D. Lamb, *Inorg. Chem.* 2005, 44, 4295). Briefly, we assume that the binding sites on AUA are independent of each other and thus, we can use a 1:1 binding isotherm of amine binding to AUA and equation 3, where \( H = \text{AUA}, G = \text{amine}, \) and \( HG = \text{AUA-amine complex}. \) There probably is some affect of the individual arms towards each others binding, but we treat this as negligible and thus we are able to calculate relative equilibrium constants.

\[
H + G \rightleftharpoons HG \quad K = \frac{[HG]}{[H][G]} \tag{3}
\]

The observed chemical shift of amine guest can be expressed as:

\[
\delta_{\text{obs}} = f_{10} \delta_G + f_{11} \delta_{HG} \tag{4}
\]

where \( f_{10} = \frac{[G]}{[G]+[HG]} \) is the fraction of free guest, \( \delta_G \) is the chemical shift of free guest, \( f_{11} = \frac{[HG]}{[G]+[HG]} \) is the fraction of host-guest complex, \( \delta_{HG} \) is the chemical shift of host-guest complex. Since \( f_{10} + f_{11} = 1 \), equation 4 can be written

\[
\delta_{\text{obs}} = (1 - f_{11}) \delta_G + f_{11} \delta_{HG} \tag{5}
\]

Defining chemical shift difference \( \Delta = \delta_{\text{obs}} - \delta_G, \Delta_{11} = \delta_{HG} - \delta_G, \) and combing equation 5 with equation 3,

\[
f_{11} = \frac{\Delta}{\Delta_{11}} = \frac{K[H]}{1 + K[H]} \tag{6}
\]

Equation 6 can be written as:
\[
\frac{\Delta}{[H]} = -K\Delta + \Delta_{11}K
\]  
(7)

To put \([H]\) in terms of total host concentration, we can use the mass balance equation:

\[
[H_i] = [HG] + [H] = [H] + \frac{\Delta}{\Delta_{11}}[G_i]
\]  
(8)

where \([H_i]\) is the total concentration of the guest.

Equation 7 can be written as:

\[
\Delta = \frac{\Delta_{11}K([H_i] - \frac{\Delta}{\Delta_{11}}[G_i])}{1 + K([H_i] - \frac{\Delta}{\Delta_{11}}[G_i])}
\]  
(9)

By preparing a plot of \(\Delta\) vs \([H_i] - \frac{\Delta}{\Delta_{11}}[G_i]\) for each amine titration and performing a nonlinear fit of the titration data using equation (9), where \(K\) and \(\Delta_{11}\) are unknown, we can determine \(K\) for each amine guest.

As the amount of amine increases, the NMR chemical shifts of the amines move back upfield to where they are when no AUA is present. We used the NMR titration data after the chemical shift of the amine had begun to return to where it was without host, the part of the titration where equilibrium exists. For primary and secondary amines, this was after two equivalents of amine and for tertiary amines this came after a quarter of an equivalent of amine. Thus, the equilibrium constants are relative to each other and represent the strength of amine association to AUA.

The equilibrium constants (log \(K\)) of AUA with amines in \(d_6\)-DMSO at 296 K are shown below:

<table>
<thead>
<tr>
<th>Amine</th>
<th>log (K)</th>
<th>Amine</th>
<th>log (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R</td>
<td>0.95</td>
<td>1S</td>
<td>0.97</td>
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<tr>
<td>2R</td>
<td>1.36</td>
<td>2S</td>
<td>0.84</td>
</tr>
<tr>
<td>3R</td>
<td>0.31</td>
<td>3S</td>
<td>0.35</td>
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