Cooperative multipoint recognition of sialic acid by benzoboroxole-based receptors bearing cationic hydrogen-bond donors

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1. Isothermal titration calorimetry binding studies

ITC experiments were performed with 2 mM receptor solution (1 and 5 - 11) and 80 mM solution of ligand (2 - 4). Five different buffers were used: 0.1 M acetate buffer (pH 5.5), 0.1 M phosphate buffer (pH 6.5), 0.1 M phosphate buffer (pH 7.4), 0.1 M ammonium acetate buffer (pH 8.5) and 0.1 M ammonium acetate (pH 10). The buffer was degassed prior to solution preparation. The pH of the solutions was adjusted with 5 M hydrochloric acid or 5 M sodium hydroxide. The solutions were filtered and degassed prior to use. ITC experiments were performed using a VP-ITC MicroCalorimeter with the parameters reported in Table S1 by titrating the ligand into the receptor solution. The experiments were performed at 25°C. The volume of the first injection for each experiment was 2 µl and it was discarded, whilst the volume of all other injections was set at 7 µl. The spacing and the reference power selected for each experiment were based on the amount of heat realised. For experiment with a small heat release (< 2.5 µcal s$^{-1}$), the spacing was set at 280 s and the reference power at 10 µcal s$^{-1}$. For titrations with large heat release (> 10 µcal s$^{-1}$), the spacing was set at 480 s and the reference power at 25 µcal s$^{-1}$. Experiments with intermediate heat release had a spacing between 300 and 380 s and a reference power of 15 - 20 µcal s$^{-1}$. Each experiment consists of 3 titrations and the heat of dilution was measured and subtracted for each experiment. The data was analysed with Origin software for ITC, fixing the number of binding sites to 1. The binding constants, enthalpy and entropy values are reported in Table S2, S3 and S4 and are the average of the three measurements, with the error calculated as twice the standard deviation.

Table S1. ITC parameters for the binding studies with VP-ITC MicroCalorimeter.

| Number of injections | 35 |
|----------------------|----|
| Cell temperature     | 25°C |
| Reference Power      | 10 – 25 µcal s$^{-1}$ |
| Initial delay        | 60 s |
| Stirring             | 307 RPM |
| Volume of each injection | 7.0 µl |
| Duration of each injection | 4.0 s |
| Spacing              | 280 – 480 s |
| Filter               | 2 |

Table S2. Isothermal titration calorimetry binding studies of receptor 1 and 2 – 10 with sialic acid (2) at pH 5.5 (0.1 M acetate buffer) at 25° C. Each experiment consists of three titrations. The heat of dilution was measured and subtracted.

| Receptor | $K_a$ (M$^{-1}$) | $\Delta H$ (kcal mol$^{-1}$) | $\Delta S$ (cal mol$^{-1}$ deg$^{-1}$) |
|----------|-----------------|--------------------------|-----------------|
| 1        | 51.2 ± 1.2      | −5.6 ± 0.1               | −10.9 ± 0.4     |
| 5        | 150.4 ± 7.9     | −3.3 ± 0.1               | −1.2 ± 0.3      |
| 6        | 234.3 ± 8.0     | −3.5 ± 0.1               | −1.0 ± 0.2      |
| 7        | 129.6 ± 0.8     | −4.9 ± 0.1               | −6.6 ± 0.2      |
| 8        | 141.0 ± 6.8     | −4.6 ± 0.2               | −5.8 ± 0.8      |
| 9        | 104.4 ± 5.2     | −3.9 ± 0.1               | −3.7 ± 0.4      |
| 10       | 110.2 ± 3.4     | −3.3 ± 0.1               | −1.8 ± 0.3      |
Table S3. Isothermal titration calorimetry binding studies of receptor 1 and 2 – 10 with sialic acid (2) at pH 7.4 (0.1 M phosphate buffer) at 25°C. Each experiment consists of three titrations. The heat of dilution was measured and subtracted.

| Receptor | $K_a$ (M$^{-1}$) | $\Delta H$ (kcal mol$^{-1}$) | $\Delta S$ (cal mol$^{-1}$ deg$^{-1}$) |
|----------|-----------------|-----------------------------|---------------------------------|
| 1        | 39.3 ± 0.6      | -4.7 ± 0.1                  | -8.3 ± 0.5                      |
| 5        | 26.8 ± 2.1      | -2.9 ± 0.1                  | -3.3 ± 0.2                      |
| 6        | 43.1 ± 4.8      | -2.8 ± 0.3                  | -2.0 ± 1.1                      |
| 7        | 43.7 ± 0.9      | -3.7 ± 0.1                  | -4.8 ± 0.4                      |
| 8        | 55.5 ± 1.0      | -2.4 ± 0.1                  | -2.6 ± 0.1                      |
| 9        | 50.5 ± 2.1      | -3.4 ± 0.1                  | -3.6 ± 0.5                      |
| 10       | 60.9 ± 4.3      | -2.9 ± 0.1                  | -1.7 ± 0.5                      |

Table S4. Isothermal titration calorimetry binding studies of receptor 1 and 2 – 10 with sialic acid (2) at pH 8.5 (0.1 M ammonium acetate buffer) at 25°C. Each experiment consists of three titrations. The heat of dilution was measured and subtracted.

| Receptor | $K_a$ (M$^{-1}$) | $\Delta H$ (kcal mol$^{-1}$) | $\Delta S$ (cal mol$^{-1}$ deg$^{-1}$) |
|----------|-----------------|-----------------------------|---------------------------------|
| 1        | 23.5 ± 2.1      | -3.5 ± 0.2                  | -5.3 ± 1.0                      |
| 5        | 21.9 ± 1.4      | -2.6 ± 0.1                  | -2.7 ± 0.5                      |
| 6        | 37.5 ± 1.0      | -2.3 ± 0.2                  | -0.5 ± 0.9                      |
| 7        | 28.1 ± 1.9      | -3.2 ± 0.1                  | -4.1 ± 0.6                      |
| 8        | 33.7 ± 1.6      | -3.4 ± 0.1                  | -4.3 ± 0.4                      |
| 9        | 36.3 ± 1.4      | -3.3 ± 0.1                  | -4.0 ± 0.4                      |
| 10       | 41.4 ± 0.6      | -2.8 ± 0.1                  | -2.0 ± 0.2                      |
Figure S1. ITC titration of 1 and 2 at pH 5.5

Figure S2. ITC titration of 5 and 2 at pH 5.5

Figure S3. ITC titration of 6 and 2 at pH 5.5

Figure S4. ITC titration of 7 and 2 at pH 5.5
Figure S5. ITC titration of 8 and 2 at pH 5.5

Figure S6. ITC titration of 9 and 2 at pH 5.5

Figure S7. ITC titration of 10 and 2 at pH 5.5

Figure S8. ITC titration of 1 and 2 at pH 7.4
Figure S9. ITC titration of 5 and 2 at pH 7.4

Figure S10. ITC titration of 6 and 2 at pH 7.4

Figure S11. ITC titration of 7 and 2 at pH 7.4

Figure S12. ITC titration of 8 and 2 at pH 7.4
Figure S13. ITC titration of 9 and 2 at pH 7.4

Figure S14. ITC titration of 10 and 2 at pH 7.4

Figure S15. ITC titration of 1 and 2 at pH 8.5

Figure S16. ITC titration of 5 and 2 at pH 8.5
Figure S17. ITC titration of 6 and 2 at pH 8.5

Figure S18. ITC titration of 7 and 2 at pH 8.5

Figure S19. ITC titration of 8 and 2 at pH 8.5

Figure S20. ITC titration of 9 and 2 at pH 8.5
Figure S21. ITC titration of 10 and 2 at pH 8.5
2. NMR spectra

Figure S22. NMR spectra of (from the bottom) the receptor 1; a 1:1 mixture of 1 and 2; a 1:2 mixture of 1 and 2; a 1:3 mixture of 1 and 2. The spectra were recorded in 0.1 M CD$_3$COOD with 30\% MeOD-d$_4$. 
Figure S23. $^1$H NMR spectrum of 6 (400 MHz, DMSO-$d_6$, 298 K)

Figure S24. $^{13}$C NMR spectrum of 6 (100 MHz, DMSO-$d_6$, 298 K)
Figure S25. $^1$H NMR spectrum of 7 (400 MHz, DMSO-$d_6$, 298 K)

Figure S26. $^{13}$C NMR spectrum of 7 (100 MHz, DMSO-$d_6$, 298 K)
Figure S27. $^1$H NMR spectrum of 8 (400 MHz, DMSO-$d_6$, 298 K)

Figure S28. $^{13}$C NMR spectrum of 8 (100 MHz, DMSO-$d_6$, 298 K)
Figure S29. $^1$H NMR spectrum of 9 (400 MHz, DMSO-$d_6$, 298 K)

Figure S30. $^{13}$C NMR spectrum of 9 (100 MHz, DMSO-$d_6$, 298 K)
Figure S31. $^1$H NMR spectrum of 10 (400 MHz, DMSO-$d_6$, 298 K)

Figure S32. $^{13}$C NMR spectrum of 10 (100 MHz, DMSO-$d_6$, 298 K)
Figure S33. $^1$H NMR spectrum of 11 (400 MHz, DMSO-$d_6$, 298 K)

Figure S34. $^{13}$C NMR spectrum of 11 (100 MHz, DMSO-$d_6$, 298 K)
Figure S35. $^1$H NMR spectrum of 13 (400 MHz, DMSO-$d_6$, 298 K)

Figure S36. $^{13}$C NMR spectrum of 13 (100 MHz, DMSO-$d_6$, 298 K)
Figure S37. $^1$H NMR spectrum of 14 (400 MHz, DMSO-$d_6$, 298 K)

Figure S38. $^{13}$C NMR spectrum of 14 (100 MHz, DMSO-$d_6$, 298 K)
Figure S39. $^1$H NMR spectrum of 15 (400 MHz, DMSO-$d_6$, 298 K)

Figure S40. $^{13}$C NMR spectrum of 15 (100 MHz, DMSO-$d_6$, 298 K)
3. MS spectra

Figure S41. ESI (-) MS of a 1:1 mixture of 1 and 2 in 0.1 M Acetate Buffer.

Figure S42. ESI (-) MS of a 1:1 mixture of 1 and 3 in 0.1 M Acetate Buffer.
4. Computational details

4.1 DFT calculations

All the DFT calculations were performed with the Gaussian program. All geometries of benzoboroxole derivatives and sialic acid were optimized by M06-2X/6-31+G(d,p), as shown in Figure 8 and Table S5.

Table S5. The calculated energies (in units of Hartree) of sialic acid (SA), receptors 1, 5-10 and their complexes as shown in Figure 8.

| Receptors | energy   | Compounds | energy   |
|-----------|----------|-----------|----------|
| SA        | -1323.219956 |           |         |
| 1         | -446.212905  | SA+1      | -1693.063746 |
| 2         | -541.211131  | SA+2      | -1788.191834 |
| 3         | -690.020457  | SA+3      | -1936.989606 |
| 4         | -749.147796  | SA+4      | -1996.138842 |
| 5         | -897.949478  | SA+5      | -2144.925071 |
| 6         | -980.112956  | SA+6      | -2227.079161 |
| 7         | -1128.920088 | SA+7      | -2375.884809 |

4.2 Solvent models: SMD calculations and MD simulations of solutions

The binding modes of the complexes were studied in both gas phase and buffered water solvents, with the results shown in Figures S43, S44, and S45. To investigate the solvent effects on the binding modes, both implicit solvent (using SMD model in Figure S43) and explicit solvent (Figures S44 and S45) models were employed.

Using the implicit SMD model (Figure S43), binding energies in of the optimized structures were greatly underestimated and did not agree with ITC experimental data. This indicates the limitations of implicit solvent model for this system.
Molecular dynamics (MD) simulations of sialic acid and benzoboroxole receptors were performed by using the Forcite module in Materials Studio package\(^1\). We selected benzoboroxole receptors \(1\) and \(5\) and carried out MD simulations of their complexation with sialic acid in both gas phase and aqueous solution. The MD simulations were run in the NVT (constant pressure and constant temperature of 298 K) ensemble with the universal force field and established periodic boundary conditions of \(a=b=c=30\ \text{Å}\), as shown in Table S6. The time step was set as 1fs, and the MD trajectory was collected during 500ps, and finally get 50 frames were used for statistical analysis. For the binding between \(1\) and sialic acid (without counterion), we obtained some similar conformations labelled as A, B, C, and D, as shown in Figure S44, and found that the boron atom is close to the \(\alpha\)-hydroxyacid rather than the glycerol chain. The minimum distance between boron atom and carboxylate was also shown in Figure S44. For the combinations of \(5\) with sialic acid, due to the presence of a positive charge in \(5\), we used counterion chloride to neutralize the periodic cell, and found some favourable conformations (A, B, C, and D) with high occurrence in MD trajectory, as shown in Figures S45. Similarly, the B atom is closer to the \(\alpha\)-hydroxyacid, which suggests that strong binding interaction between them. We also carried out MD simulations of the possible conformations of complexes \(1-2\) (Figure S44) and \(5-2\) (Figure S45) in aqueous solution. It can be seen that B atom is also closer to the \(\alpha\)-hydroxyacid, similar to that in gas phase.

**Table S6.** Simulation models for molecular dynamics simulations of the investigated systems.

| Studied systems     | Solute            | Solvent molecules | The size of periodic box | Ions                                      |
|---------------------|-------------------|-------------------|--------------------------|-------------------------------------------|
| sialic acid & receptor \(1\) | sialic acid and \(1\) | Gas phase        | 30\(\text{Å}\) x 30\(\text{Å}\) x 30\(\text{Å}\) | None                                      |
| sialic acid & receptor \(5\) | sialic acid and \(5\) | Gas phase        | 30\(\text{Å}\) x 30\(\text{Å}\) x 30\(\text{Å}\) | One amino and one chloride ion           |
| sialic acid & receptor \(1\) | sialic acid and \(1\) | Aqueous solution (100 water molecules) | 30\(\text{Å}\) x 30\(\text{Å}\) x 30\(\text{Å}\) | None                                      |
| sialic acid & receptor \(5\) | sialic acid and \(5\) | Aqueous solution (100 water molecules) | 30\(\text{Å}\) x 30\(\text{Å}\) x 30\(\text{Å}\) | One amino and one chloride ion           |
Figure S44. Conformations of complex 1-2 taken from MD trajectories without and with water solvent molecules. Intermolecular distance is also shown. The light blue, pink and dark blue balls represent the B, O and N atoms, respectively.
Figure S45. Conformations of complex 5-2 taken from MD trajectories without and with water solvent molecules. Intermolecular distance is also shown. The light blue, pink, dark blue, and light green balls represent the B, O, N and Cl atoms, respectively.

4.3 Coordinate files

Cartesian coordinates of the optimized geometries are listed as follows.

|      | X       | Y       | Z       |
|------|---------|---------|---------|
| C    | 0.12289 | -0.0691 | 0.61115 |
| C    | 0.84526 | -2.30837| 0.09438 |
| C    | 0.1165  | -3.10689| -0.06899|
| C    | 0.85312 | -1.68044| -1.95963|
| H    | 1.56862 | -2.64261| 0.84902 |
| H    | 1.04459 | -0.60078| 0.77294 |
| O    | 1.10769 | -1.04371| 0.0581  |
| O    | 1.28436 | 0.8193  | -1.14769|
| O    | 1.20251 | 2.00101 | 0.98379 |

SA (the number of imaginary frequencies=0)
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| H | -0.97427 | -0.74236 | -0.16354 | O | -0.97427 | -0.74236 | -0.16354 |
| C | -0.43885 | -1.28997 | 2.07259 | O | -0.43885 | -1.28997 | 2.07259 |
| O | 3.37936 | 0.88553 | 1.48827 | O | 3.37936 | 0.88553 | 1.48827 |
| O | 1.10525 | 2.87182 | 0.90041 | O | 1.10525 | 2.87182 | 0.90041 |
| C | 2.45565 | 3.59462 | -0.91325 | C | 2.45565 | 3.59462 | -0.91325 |
| H | 3.37623 | 3.60144 | -1.3147 | H | 3.37623 | 3.60144 | -1.3147 |
| H | 2.15508 | 4.62979 | -0.69795 | H | 2.15508 | 4.62979 | -0.69795 |
| O | 1.55027 | 3.01493 | -1.85335 | O | 1.55027 | 3.01493 | -1.85335 |
| H | 1.56101 | 3.52202 | -2.67197 | H | 1.56101 | 3.52202 | -2.67197 |
| N | 3.73376 | -1.31136 | -0.19152 | N | 3.73376 | -1.31136 | -0.19152 |
| H | 3.84331 | -0.80343 | 0.49813 | O | 1.74514 | 0.57193 | -0.55562 |
| H | 2.93709 | -0.51472 | -1.96305 | B | 0.81195 | 1.54017 | -0.15531 |
| C | 4.95888 | -1.66063 | -0.71862 | O | 1.14574 | 2.80074 | 0.11086 |
| O | 5.91773 | -1.84547 | 0.015 | O | 2.05475 | 3.05235 | -0.10076 |
| C | 5.08322 | -1.8212 | -2.22344 | C | 1.78681 | -1.76054 | -0.10391 |
| H | 4.24345 | -2.35812 | -2.66794 | H | 1.29567 | -2.72627 | -0.22794 |
| H | 5.12092 | -2.84292 | -2.67807 | H | 2.84388 | -1.83358 | -0.36156 |
| H | 6.02011 | -2.33575 | -2.42745 | N | 1.70743 | -1.37724 | 1.35064 |
| H | 0.84869 | 1.9962 | 2.13102 | H | 2.17726 | -2.04004 | 1.97223 |
| Na | 2.19813 | -0.25413 | 2.82545 | H | 2.13843 | -0.44863 | 1.44999 |
| H | -1.86096 | -0.88535 | 0.17548 | H | 0.71957 | -1.28796 | 1.62841 |
| H | 6.02011 | -2.33575 | -2.42745 | O | 1.90466 | -1.96762 | 0.42068 |
| C | -0.37984 | 0.49553 | -0.00002 | C | 0.75662 | 0.63031 | 0.00197 |
| C | -0.32969 | 0.84142 | 0.00005 | C | -1.33013 | -0.58753 | 0.28086 |
| C | -1.67597 | 1.19165 | 0.00007 | C | -2.03696 | -1.78396 | 0.23561 |
| C | 1.73888 | 2.37186 | 0.00001 | O | -3.17887 | -1.72941 | -0.39845 |
| C | 2.22631 | -1.17563 | -0.00008 | C | -0.70776 | -0.19044 | -0.39333 |
| C | 0.8785 | -1.51093 | -0.0001 | C | -3.29393 | 0.60863 | -0.33679 |
| C | -0.6768 | 1.75177 | 0.00009 | C | 0.12944 | -0.3877 | 0.62754 |
| H | 1.9905 | 2.24615 | 0.00012 | H | 1.60266 | -1.73675 | 0.47065 |
| H | 3.67962 | 0.41468 | 0.0001 | H | 3.96423 | -2.64602 | -0.15161 |
| H | 2.99221 | -1.95244 | -0.00013 | H | -5.05972 | 0.49646 | -0.66507 |
| H | 0.57126 | -2.55314 | -0.00016 | H | -3.77302 | 1.6277 | -0.5513 |
| O | -2.09194 | 0.80955 | 0.00005 | O | 0.369 | 1.02549 | 0.51198 |
| O | -1.63622 | -0.4244 | 0.00001 | B | -0.82114 | 1.60851 | 0.18471 |
| O | -2.5392 | -1.44101 | -0.00007 | O | -0.89323 | 0.305 | 0.66763 |
| H | -3.43973 | -1.11499 | -0.00006 | H | -0.09848 | 3.52086 | 0.13125 |
| H | -0.91056 | 2.39046 | -0.88645 | C | 1.04479 | -1.14528 | -0.33276 |
| H | -0.91056 | 2.39046 | -0.88645 | O | 0.60852 | -2.17664 | -0.42137 |

The number of imaginary frequencies: 0
| Symbol | X       | Y       | Z       |
|--------|---------|---------|---------|
| H      | -2.39059 | 2.95442 | -0.09922 |
| H      | -5.55159 | 2.18429 | 0.41068  |
| H      | -7.25774 | 0.37893 | 0.44712  |
| H      | -6.6305  | -1.94447| -0.08858 |
| H      | -4.29316 | -2.52423| -0.67428 |
| C      | -5.27254 | 1.16163 | 0.17625  |
| C      | -6.22737 | 0.14918 | 0.19651  |
| C      | -5.87181 | -1.16861| -0.10671 |
| C      | -3.53134 | 0.46789 | 2.57526  |
| H      | -0.56879 | -0.0824 | 1.56068  |
| H      | -1.07957 | 3.38257 | -1.18496 |
| H      | 2.1846   | -1.64624| -0.73507 |
| C      | 1.90724  | -2.82826| -0.88753 |
| H      | 1.36053  | 0.2292 | -0.56597 |
| O      | 3.61489  | -1.11616| -0.90326 |
| O      | 3.92015  | -1.30796| -1.93243 |
| H      | 4.25187  | -1.72447| -0.45426 |
| H      | 3.84012  | 0.30645| -0.62693 |
| H      | 4.14204  | 0.89388 | -1.19209 |
| C      | 3.92997  | 0.80289 | 0.60589  |
| H      | 3.34477  | 0.19385| 1.62213  |
| H      | 2.54647  | -0.40741| 1.42916  |
| N      | 4.60605  | 1.95496 | 0.80335  |
| C      | 4.50052  | 2.48031| 1.6603   |
| H      | 5.27175  | 2.29391| 0.12723  |
| H      | -1.87967 | 1.74184 | -0.49513 |
| H      | -1.93413 | 2.94077 | -1.09312 |
| H      | -1.07957 | 3.38257 | -1.18496 |
| H      | -0.56879 | -0.0824 | 1.56068  |
| C      | 3.53134  | 0.46789 | 2.57526  |
| C      | -3.85421 | 0.84837 | -0.15079 |
| C      | -3.65151 | -0.47366 | -0.48141 |
| C      | -4.55222 | -1.49797| -0.43393 |
| C      | -5.87181 | -1.16861| -0.10671 |
| C      | -6.22737 | 0.14918 | 0.19651  |
| C      | -5.27254 | 1.16163 | 0.17625  |
| C      | -2.13317 | -0.57524| -0.73802 |
| C      | -4.29316 | -2.52423| -0.67428 |
| C      | -6.6305  | -1.94447| -0.08588 |
| H      | -7.25774 | 0.37893 | 0.44712  |
| H      | -5.55159 | 2.18429 | 0.41068  |
| O      | -1.62372 | 0.75447 | -0.67658 |
| O      | -2.39059 | 2.95442 | -0.09922 |

The number of imaginary frequencies: 0

SAI: The number of imaginary frequencies: 0
C -4.90486 3.41609 1.60074  B -2.06113 0.20302 1.20064  C -10.05037 -1.3385 2.43875
C -3.57445 3.75279 1.99193  C -4.4032 -1.28939 1.09035  H -7.96306 -1.11936 2.66878
C -2.54721 2.79238 1.89081  N -5.91402 -1.16319 1.37057  C -10.38786 -1.99403 0.15809
C -4.01042 -0.14252 0.17727  H -6.23415 -0.71274 2.20649  H -8.43967 -2.32788 -1.13617
H -6.16705 1.88641 0.71876  C -6.78619 -1.69525 0.48498  C -11.00232 -1.62262 1.45338
H -5.69743 4.12961 1.73356  O -6.37092 -2.10829 -0.62513  H -10.35993 -1.09684 3.43481
H -3.35416 4.72833 2.36622  C -8.28013 -1.68796 0.82494  H -11.31289 -2.24163 -0.59923
H -1.54047 3.00768 2.18732  C -8.69168 -1.35739 2.12048  C -12.50013 -1.52103 1.8013
O -2.56444 -0.35332 -0.12033  C -9.22283 -2.03634 -0.1532  H -12.61873 -0.86566 2.6412
H -13.0306 -1.12483 0.90482  N -14.88859 -4.27443 2.07324  H -16.05615 -2.24481 1.13138
N -13.05655 -2.84542 2.12049  H -15.85242 -4.43293 1.85435  H -14.69285 -1.17703 1.21114
H -4.31453 -2.22188 0.50313  H -14.33677 -5.01356 2.45542  H -4.59983 -0.1547 -0.70898
H -3.9322 1.26992 2.0064  C -14.34387 -3.07209 1.85204  H 2.07122 -1.24858 -3.21674
H -12.47344 -3.55462 2.52178  N -15.09367 -2.08251 1.35637

References

[1] Materials studio, Version 4.0; Accelrys, Inc.: San Diego, 2006.