Triazole Functionalized Acyclic Cucurbit[n]uril-Type Receptors: Host•Guest Recognition Properties

Supporting Information

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Synthetic procedures and characterization data

**Compound 3.** Ascorbic acid (28 mg, 0.16 mmol), NaOH (8 mg, 0.16 mmol) and CuSO₄ (8 mg, 0.04 mmol) were mixed and then dissolved in a mixture of H₂O and EtOH (4 mL, 1:1). Alkyne host 7 (104 mg, 0.096 mmol) and sodium 3-azidopropene-1-sulfonate 8b (144.5 mg, 0.773 mmol) were added as solid. The mixture was heated with microwave at 80 °C for 30 min, and then solid was removed by using centrifuge. EtOH (5 ml) was added into the liquid and the crude product could precipitate. The product was recrystallized with EtOH (3 mL) and H₂O (1 mL). A white solid was obtained after drying under high vacuum (82 mg, 45.8%). M.p. > 316 °C (decomposed). IR (ATR, cm⁻¹): 3440, 1721, 1472, 1234, 1314, 1211, 1086, 1038, 1011, 845, 797, 757, 731. ¹H NMR (600 MHz, D₂O): 8.05 (s, 4H), 6.78 (s, 4H), 5.64 (d, J = 15.6, 4H), 5.41 (d, J = 9.0, 2H), 5.36 (s, 2H), 5.22 (s, 4H), 5.02 (s, 4H), 4.92 (s, 2H), 4.50 (m, 8H), 4.25 (d, J = 15.6, 4H), 4.14 (d, J = 15.6, 4H), 4.08 (d, J = 15.2, 2H), 2.87 (m, 8H), 2.32 (m, 8H), 1.75 (s, 6H), 1.70 (s, 6H). ¹³C NMR (100 MHz, D₂O, 1, 4-dioxane as internal reference): δ 156.7, 156.0, 150.0, 128.2, 125.9, 115.4, 84.4, 78.6, 77.6, 71.1, 63.6, 52.7, 50.0, 49.0, 48.5, 47.8, 35.1, 25.2, 16.2, 15.1. HRMS (ESI, negative): m/z 887.2331 ([M + 2H – 4Na]⁺), calculated 887.2319.

**Compound 4.** Ascorbic acid (28 mg, 0.16 mmol), NaOH (8 mg, 0.16 mmol) and CuSO₄ (8 mg, 0.04 mmol) were mixed and then dissolved in a mixture of H₂O and EtOH (4 mL, 1:1). Alkyne host 7 (104 mg, 0.096 mmol) and sodium 4-azidobutane-1-sulfonate 8c (155.4 mg, 0.773 mmol) were added as solid. The mixture was heated with microwave at 80 °C for 30 min, and then solid was removed by using centrifuge. EtOH (5 ml) was added into the liquid and the crude product could precipitate. The product was recrystallized with EtOH (3 mL) and H₂O (1 mL). A white solid was obtained after drying under high vacuum (52 mg, 28.3%). M.p. > 305 °C (decomposed). IR (ATR, cm⁻¹): 3407, 1722, 1469, 1425, 1379, 1314, 1230, 1179, 1085, 1009, 975, 845, 797, 757, 667. ¹H NMR (600 MHz, D₂O): 7.97 (s, 4H), 6.84 (s, 4H), 5.67 (d, J = 15.6, 2H), 5.57 (d, J = 15.6, 4H), 5.44 (d, J = 8.4, 2H), 5.38 (d, J = 9, 2H), 5.22 (d, J = 16.2, 4H), 5.06 (d, J = 12, 4H), 4.99 (d, J = 12, 2H), 4.34 (m, 8H), 4.26 (d, J = 15.6, 4H), 4.12 (d, J = 16.8, 6H), 2.87 (m, 8H), 1.91 (m, 8H), 1.77 (s, 6H), 1.69 (s, 6H), 1.66 (m, 8H). ¹³C NMR (100 MHz, D₂O, 1, 4-dioxane as internal reference): δ 157.2, 156.6, 150.4, 144.1, 129.1, 125.8, 116.6, 79.3, 78.1, 72.1, 71.9, 64.2, 50.8, 50.4, 49.1, 35.7, 29.0, 21.8, 16.8, 15.7. HRMS (ESI, negative): m/z 915.2599 ([M + 2H – 4Na]⁺), calculated 915.2632.
**Compound 7.** To a solution of (1.70 g, 2.18 mol) in TFA (5 mL) was added 1,4-bis(prop-2-yn-1-yl oxy)benzene 6 (1.62 g, 8.71 mmol). The solution was heated at 50 °C for 4 h. The solvent was removed by rotary evaporation. The crude product was further dried on high vacuum and then washed with water (50 mL). The solid was washed with acetone (2 x 50 mL) and filtered. The resulting solid was dissolved in concentrated HCl (50 mL) and then precipitated by adding water (100 mL) to yield a white solid (1.1 g, 1.0 mmol, 45%). M.p. > 260 °C (decomposed). IR (ATR, cm⁻¹): 2939w, 1721m, 1463m, 1380m, 1314w, 1231m, 1211m, 1186m, 1090m, 941s, 848w, 796m, 758m, 616m. ¹H NMR (400 MHz, D₂O): 6.92 (s, 4H), 5.54 (d, J=14.9, 2H), 5.45 (d, J=15.0, 4H), 5.34 (d, J=9.0, 2H), 5.23 (d, J=9.0, 2H), 5.15 (d, J=15.8, 4H), 4.79 (d, J=15.0, 4H), 4.72 (d, J=15.0, 4H), 4.10 (d, J=15.8, 4H), 4.03 (d, J=15.0, 4H), 4.03 (d, J=14.9, 2H), 3.52 (s, 4H), 1.65 (s, 6H), 1.61 (s, 6H). ¹³C NMR (125 MHz, DMSO-d6): 156.6, 155.2, 150.7, 129.6, 115.6, 81.3, 79.1, 78.5, 77.5, 71.9, 71.5, 59.0, 54.2, 49.4, 35.6, 18.0, 16.9. HR-MS (ESI): m/z 1117.4007 ([M+H]+), calculated 1117.4029.
$^1$H and $^{13}$C NMR spectra of new compounds

Figure S1. $^1$H NMR of 2 recorded on 600 MHz in D$_2$O.
Figure S2. $^1$H NMR of 2 recorded on 600 MHz in D2O.
Figure S3. $^{13}$C NMR of 2 recorded on 100 MHz in D$_2$O (1,4-dioxane as internal reference).
Figure S4. $^1$H NMR of 3 recorded on 600 MHz in D2O.
Figure S5. $^{13}$C NMR of 3 recorded on 100 MHz in D$_2$O (1,4-dioxane as internal reference).
Figure S6. $^1$H NMR of 4 recorded on 600 MHz in D2O.
Figure S7. $^{13}$C NMR of 4 recorded on 100 MHz in D$_2$O (1,4-dioxane as internal reference).
Figure S8. $^1$H NMR of 7 recorded at 400 MHz in DMSO-$d_6$. 
Figure S9. $^{13}$C NMR of 7 recorded at 125 MHz in DMSO-$d_6$. 
Figure S10. $^1$H NMR spectra (600 MHz, D$_2$O, 298K) recorded for the dilution of host 2 (8.0 - 0.1 mM). Host 2 itself weakly self-associated in water, which is evidenced by the upfield chemical shift changes of the aromatic region at 8.03 - 8.18 ppm protons.
Self-association Model Used in Scientist.

// Micromath Scientist Model File
// self-association model for NMR
IndVars: concTot
DepVars: DeltaObs
Params: Ka, Deltasat, Deltazero
Ka = concBound/(concFree*concFree)
concTot = concFree + concBound/2
DeltaObs = Deltazero + (Deltasat - Deltazero) * (1/2*concBound/concTot)
//Constraints
0 < Ka
0 < concFree < concTot
0 < concBound < concTot
***

Figure S11. Plot of chemical shift of 2 versus [2]. The solid line represents the best non-linear fitting of the data to a two-fold self-association model with Ka = 299 M\(^{-1}\).
Figure S12. $^1$H NMR spectra (600 MHz, D$_2$O, 298K) recorded for the dilution of host 3 (10.0 - 0.1 mM). Host 3 itself weakly self-associated in water, which is evidenced by the upfield chemical shift changes of the aromatic region at 8.02 - 8.20 ppm protons.
Figure S13. Plot of chemical shift of 3 versus [3]. The solid line represents the best non-linear fitting of the data to a two-fold self-association model with $K_a = 903 \text{ M}^{-1}$. 
Figure S14. $^1$H NMR spectra (600 MHz, D$_2$O, 298K) recorded for the dilution of host 4 (8.0 – 0.1 mM). Host 4 itself weakly self-associated in water, which is evidenced by the upfield chemical shift changes of the aromatic region at 6.84 – 6.91 ppm protons.
Figure S15. Plot of chemical shift of 4 versus [4]. The solid line represents the best non-linear fitting of the data to a two-fold self-association model with $K_a = 546 \text{ M}^{-1}$. 
$^1$H NMR spectra of selected guests with hosts 1

*Figure S16.* $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 2, b) 17, c) an equimolar mixture of 2 and 17 (1 mM), and d) a 2:1 mixture of 17 (2 mM) and 2 (1 mM).
Figure S17. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 2, b) 9, c) an equimolar mixture of 2 and 9 (1 mM), and d) a 2:1 mixture of 9 (2 mM) and 2 (1 mM).
Figure S18. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 2, b) 19, c) an equimolar mixture of 2 and 19 (1 mM), and d) a 2:1 mixture of 19 (2 mM) and 2 (1 mM).
Figure S19. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 2, b) 15, c) an equimolar mixture of 2 and 15 (1 mM), and d) a 2:1 mixture of 15 (2 mM) and 2 (1 mM).
Figure S20. ^1^H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 2, b) 20, c) an equimolar mixture of 2 and 20 (1 mM), and d) a 2:1 mixture of 20 (2 mM) and 2 (1 mM).
**Figure S21.** $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 3, b) 17, c) an equimolar mixture of 3 and 17 (1 mM), and d) a 2:1 mixture of 17 (2 mM) and 3 (1 mM).
Figure S22. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 3, b) 9, c) an equimolar mixture of 3 and 9 (1 mM), and d) a 2:1 mixture of 9 (2 mM) and 3 (1 mM).
Figure S23. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 3, b) 19, c) an equimolar mixture of 3 and 19 (1 mM), and d) a 2:1 mixture of 19 (2 mM) and 3 (1 mM).
Figure S24. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 3, b) 15, c) an equimolar mixture of 3 and 15 (1 mM), and d) a 2:1 mixture of 15 (2 mM) and 3 (1 mM).
Figure S25. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 3, b) 20, c) an equimolar mixture of 3 and 20 (1 mM), and d) a 2:1 mixture of 20 (2 mM) and 3 (1 mM).
Figure S26. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 4, b) 17, c) an equimolar mixture of 4 and 17 (1 mM), and d) a 2:1 mixture of 17 (2 mM) and 4 (1 mM).
Figure S27. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 4, b) 9, c) an equimolar mixture of 4 and 9 (1 mM), and d) a 2:1 mixture of 9 (2 mM) and 4 (1 mM).
Figure S28. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 4, b) 19, c) an equimolar mixture of 4 and 19 (1 mM), and d) a 2:1 mixture of 19 (2 mM) and 4 (1 mM).
Figure S29. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 4, b) 15, c) an equimolar mixture of 4 and 15 (1 mM), and d) a 2:1 mixture of 15 (2 mM) and 4 (1 mM).
Figure S30. $^1$H NMR spectra recorded (600 MHz, RT, 20 mM phosphate-buffered D$_2$O) for: a) 4, b) 20, c) an equimolar mixture of 4 and 20 (1 mM), and d) a 2:1 mixture of 20 (2 mM) and 4 (1 mM).
Determination of $K_a$ between various hosts and drugs of abuse using Isothermal Titration Calorimetry (ITC).

All ITC experiments were conducted in the 200 µL working volume of the sample cell of the PEAQ ITC instrument. We used an injection syringe of 40 µL capacity. In each case, the host and guest solutions were prepared in a 20 mM NaH$_2$PO$_4$ buffer (pH 7.4). The sample cell was filled to capacity (200 µL) with the host solution and the guest solution was titrated in (first injection = 0.4µL, subsequent 18 injections = 2 µL). The binding data was fitted using the 1:1 binding model in MicroCal PEAQ-ITC analysis software.
**Figure S31.** a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 9 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.05± 0.07) × 10⁶ M⁻¹, ΔH = - 5.97 ± 0.021 kcal/mol, -TΔS = -2.65 kcal/mol).
**Figure S32.** a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 10 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.39 \pm 0.36) \times 10^5$ M$^{-1}$, $\Delta H = -8.76 \pm 0.750$ kcal/mol, $-T\Delta S = 1.74$ kcal/mol).
Figure S33. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 11 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.79\pm 0.09) \times 10^6$ M$^{-1}$, $\Delta H = - 9.09 \pm 0.043$ kcal/mol, $-T\Delta S = 0.559$ kcal/mol).
**Figure S34.** a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 12 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.51 ± 0.16) × 10$^6$ M$^{-1}$, ΔH = -9.30 ± 0.034 kcal/mol, -TΔS = 0.569 kcal/mol).
Figure S35. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 13 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (3.73± 0.09) × 10⁵ M⁻¹, ΔH = - 4.98 ± 0.025 kcal/mol, -TΔS = -2.63 kcal/mol).
Figure S36. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 14 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (1.51 ± 0.24) × 10^6 M$^{-1}$, ΔH = -9.89 ± 0.198 kcal/mol, -TΔS = 1.46 kcal/mol).
Figure S37. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 15 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (8.62 \pm 0.27) \times 10^5$ M$^{-1}$, $\Delta H = -6.87 \pm 0.027$ kcal/mol, $-T\Delta S = -1.24$ kcal/mol).
Figure S38. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 16 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.12 \pm 0.05) \times 10^6$ M$^{-1}$, $\Delta H = -7.43 \pm 0.040$ kcal/mol, -$\Delta S = -0.828$ kcal/mol).
Figure S39. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 17 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (3.34± 0.19) × 10⁶ M⁻¹, ΔH = - 9.74 ± 0.045 kcal/mol, -TΔS = - 0.841 kcal/mol).
Figure S40. a) Plot of DP vs time from the titration of molecular container 2 (100 μM) and with guest 18 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (3.72± 0.61) \times 10^6 M⁻¹, ΔH = - 11.7 ± 0.167 kcal/mol, -TΔS = 2.78 kcal/mol).
**Figure S41.** a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 19 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (3.38± 0.33) × 10$^6$ M$^{-1}$, ΔH = - 10.0 ± 0.084 kcal/mol, -TΔS = - 1.10 kcal/mol).
Figure S42. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 20 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.63± 0.07) × 10⁵ M⁻¹, ΔH = - 4.61 ± 0.047 kcal/mol, -TΔS = - 2.51 kcal/mol).
Figure S43. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with guest 21 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.02± 0.04) × 10$^6$ M$^{-1}$, ΔH = - 8.13 ± 0.036 kcal/mol, -TΔS = - 0.068 kcal/mol).
Figure S44. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 9 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.72± 0.17) × 10⁶ M⁻¹, ΔH = - 6.03 ± 0.065 kcal/mol, -TΔS = - 2.48 kcal/mol).
Figure S45. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 10 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.26± 0.24) × 10$^5$ M$^{-1}$, $\Delta H = -8.10 \pm 0.481$ kcal/mol, -T$\Delta S = 1.14$ kcal/mol).
Figure S46. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 11 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.83 \pm 0.09) \times 10^6$ M$^{-1}$, $\Delta H = -8.95 \pm 0.044$ kcal/mol, $-T\Delta S = 0.397$ kcal/mol).
Figure S4. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 12 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.86± 0.17) × 10$^6$ M$^{-1}$, ΔH = - 9.23 ± 0.047 kcal/mol, -TΔS = 0.423 kcal/mol).
Figure S48. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 13 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (4.00± 0.13) × 10$^5$ M$^{-1}$, ΔH = - 5.13 ± 0.032 kcal/mol, -TΔS = - 2.51 kcal/mol).
Figure S49. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 14 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.53± 0.17) × 10⁶ M⁻¹, ΔH = - 8.95 ± 0.054 kcal/mol, -TΔS = - 0.211 kcal/mol).
Figure S50. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 15 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (8.20± 0.27) × 10$^5$ M$^{-1}$, ΔH = - 6.54 ± 0.027 kcal/mol, -TΔS = - 1.53 kcal/mol).
Figure S51. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 16 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (9.52± 0.68) × 10^5 M$^{-1}$, ΔH = - 7.44 ± 0.067 kcal/mol, -TΔS = - 0.720 kcal/mol).
Figure S52. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 17 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.01± 0.09) × 10$^6$ M$^{-1}$, ΔH = - 6.26 ± 0.030 kcal/mol, -TΔS = - 2.34 kcal/mol).
Figure S53. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 18 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (3.24± 0.18) × 10^6 M$^{-1}$, ΔH = - 11.8 ± 0.054 kcal/mol, -TΔS = 2.91 kcal/mol).
Figure S54. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 19 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (9.62 \pm 0.38) \times 10^5$ M$^{-1}$, $\Delta H = -10.0 \pm 0.047$ kcal/mol, $-T\Delta S = 1.86$ kcal/mol).
Figure S55. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 20 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.57± 0.07) × 10⁵ M⁻¹, ΔH = - 4.60 ± 0.051 kcal/mol, -TΔS = - 2.49 kcal/mol).
Figure S56. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with guest 21 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta$H as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.04 \pm 0.03) \times 10^6$ M$^{-1}$, $\Delta H = -8.14 \pm 0.018$ kcal/mol, $-T\Delta S = -0.070$ kcal/mol).
Figure S5. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 9 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.13± 0.04) × 10⁶ M⁻¹, ΔH = - 5.64 ± 0.021 kcal/mol, -TΔS = - 2.62 kcal/mol).
Figure S58. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 10 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (8.55 \pm 1.04) \times 10^4 \text{ M}^{-1}$, $\Delta H = -6.22 \pm 0.263 \text{ kcal/mol}$, -$\Delta S = -0.508 \text{ kcal/mol}$).
Figure S59. a) Plot of DP vs time from the titration of molecular container 4 (100 μM) and with guest 11 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = $(6.33 \pm 0.15) \times 10^5$ M$^{-1}$, $\Delta H = -7.85 \pm 0.026$ kcal/mol, $-T\Delta S = -0.073$ kcal/mol).
Figure S60. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 12 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.24± 0.07) × 10⁶ M⁻¹, ΔH = - 8.03 ± 0.054 kcal/mol, -TΔS = - 0.278 kcal/mol).
Figure S61. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 13 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (2.15 ± 0.06) × 10^5 M$^{-1}$, ΔH = - 4.89 ± 0.028 kcal/mol, -TΔS = - 2.39 kcal/mol).
Figure S6. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 14 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.27± 0.09) × 10⁶ M⁻¹, ΔH = - 8.44 ± 0.069 kcal/mol, -TΔS = 0.112 kcal/mol).
Figure S63. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 15 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (2.99 \pm 0.06) \times 10^5$ M$^{-1}$, $\Delta H = -5.82 \pm 0.022$ kcal/mol, -$\Delta S = -1.65$ kcal/mol).
Figure S64. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 16 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (4.37 \pm 0.17) \times 10^5$ M$^{-1}$, $\Delta H = -6.79 \pm 0.044$ kcal/mol, $-T\Delta S = -0.912$ kcal/mol).
Figure S65. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 17 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (K_a = (2.03± 0.06) × 10⁶ M⁻¹, ΔH = - 8.74 ± 0.024 kcal/mol, -TΔS = 0.136 kcal/mol).
Figure S6  a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 18 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.05± 0.07) × 10$^6$ M$^{-1}$, ΔH = -10.5 ± 0.035 kcal/mol, -TΔS = 1.93 kcal/mol).
Figure S6: a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 19 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.77± 0.07) × 10⁶ M⁻¹, ΔH = - 9.07 ± 0.039 kcal/mol, -TΔS = 0.543 kcal/mol).
Figure S6 a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 20 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (8.47 ± 0.82) × 10$^4$M$^{-1}$, ΔH = -3.88 ± 0.124 kcal/mol, -TΔS = -2.84 kcal/mol).
Figure S69 a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with guest 21 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (5.15± 0.58) $\times$ 10$^5$M$^{-1}$, ΔH = - 7.24 ± 0.055 kcal/mol, -TΔS = -0.548 kcal/mol).
Figure S70. a) Plot of DP vs time from the titration of molecular container **Motor 1** (100 µM) and Butylamine Hydrochloride (200 µM) with guest 9 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (5.05± 0.31) × 10⁷ M⁻¹, ΔH = - 6.23 ± 0.01 kcal/mol, -TΔS = -4.28 kcal/mol).
Figure S71. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and with guest 10 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.82± 0.09) × 10⁶ M⁻¹, ΔH = - 7.61 ± 0.04 kcal/mol, -TΔS = -0.926 kcal/mol).
Figure S72. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and Butylamine Hydrochloride (500 µM) with guest 11 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.73 \pm 0.20) \times 10^7$ M$^{-1}$, $\Delta H = -7.59 \pm 0.10$ kcal/mol, $-T\Delta S = -2.29$ kcal/mol).
Figure S7. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and Butylamine Hydrochloride (500 µM) with guest 12 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (8.93± 0.33) × 10⁷ M⁻¹, ΔH = - 9.35 ± 0.02 kcal/mol, -TΔS = -1.50 kcal/mol).
Figure S74. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and with guest 13 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.24 \pm 0.06) \times 10^6$ M$^{-1}$, $\Delta H = -5.67 \pm 0.03$ kcal/mol, $-T\Delta S = -2.65$ kcal/mol).
Figure S75. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and Butylamine Hydrochloride (1.00 mM) with guest 14 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (2.02 \pm 0.22) \times 10^8$ M$^{-1}$, $\Delta H = -8.01 \pm 0.05$ kcal/mol, $-T\Delta S = -3.33$ kcal/mol).
Figure S7. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and with guest 15 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.95± 0.09) × 10⁶ M⁻¹, ΔH = - 5.70 ± 0.03 kcal/mol, -TΔS = -2.88 kcal/mol).
Figure S7. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and Butylamine Hydrochloride (500 µM) with guest 16 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ∆H as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (2.25± 0.08) × 10$^7$ M$^{-1}$, ∆H = - 8.37 ± 0.03 kcal/mol, -T∆S = -1.66 kcal/mol).
Figure S7. a) Plot of DP vs time from the titration of molecular container *Motor 1* (100 µM) and Butylamine Hydrochloride (500 µM) with guest 17 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.67± 0.08) × 10$^8$ M$^{-1}$, ΔH = -8.09 ± 0.02 kcal/mol, -TΔS = -3.13 kcal/mol).
**Figure S79.** a) Plot of DP vs time from the titration of molecular container **Motor 1** (100 µM) and Butylamine Hydrochloride (500 µM) with guest 18 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.78± 0.07) × 10$^8$ M$^{-1}$, ΔH = - 11.4 ± 0.02 kcal/mol, -TΔS = 0.099 kcal/mol).
Figure S80. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 μM) and Butylamine Hydrochloride (1.00 mM) with guest 19 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (4.69 ± 0.22) × 10⁸ M⁻¹, ΔH = -12.3± 0.03 kcal/mol, -TΔS = 0.507 kcal/mol).
**Figure S81.** a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and with guest 20 (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (9.62 \pm 0.34) \times 10^5$ M$^{-1}$, $\Delta H = -6.55 \pm 0.03$ kcal/mol, $-T\Delta S = -1.61$ kcal/mol).
Figure S8. a) Plot of DP vs time from the titration of molecular container Motor 1 (100 µM) and Butylamine Hydrochloride (500 µM) with guest 21 (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.70 ± 0.05) × 10⁷ M⁻¹, ΔH = - 9.09 ± 0.03 kcal/mol, -TΔS = -0.781 kcal/mol).
**Figure S8.** a) Plot of DP vs time from the titration of molecular container **Motor 1** (100 µM) and with Butylamine Hydrochloride (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.75 ± 0.08) × 10⁵ M⁻¹, ΔH = -4.86 ± 0.048 kcal/mol, -TΔS = -2.28 kcal/mol).
Figure S84. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with methamphetamine (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = $(7.35 \pm 0.43) \times 10^5$ M$^{-1}$, ΔH = -7.99 ± 0.066 kcal/mol, -TΔS = -0.021 kcal/mol).
Figure S85. a) Plot of DP vs time from the titration of molecular container 2 (100 µM) and with fentanyl (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta$H as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.31 \pm 0.09) \times 10^6$ M$^{-1}$, $\Delta H = -9.55 \pm 0.080$ kcal/mol, $-T\Delta S = 1.20$ kcal/mol).
Figure S86. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with methamphetamine (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (6.94 ± 0.32) × 10⁵ M⁻¹, ΔH = -8.03 ± 0.055 kcal/mol, -TΔS = 0.064 kcal/mol).
Figure S87. a) Plot of DP vs time from the titration of molecular container 3 (100 µM) and with fentanyl (1.00 mM) in 20 mM NaH$_2$PO$_4$ buffer (pH 7.4); b) plot of the $\Delta H$ as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model ($K_a = (1.15 \pm 0.07) \times 10^6$ M$^{-1}$, $\Delta H = -9.12 \pm 0.076$ kcal/mol, -$T\Delta S = 0.850$ kcal/mol).
Figure S88. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with methamphetamine (1.00 mM) in 20 mM NaH₂PO₄ buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (5.35 ± 0.18) × 10⁵ M⁻¹, ΔH = -7.56 ± 0.038 kcal/mol, -TΔS = -0.259 kcal/mol).
Figure S89. a) Plot of DP vs time from the titration of molecular container 4 (100 µM) and with fentanyl (1.00 mM) in 20 mM NaH2PO4 buffer (pH 7.4); b) plot of the ΔH as a function of molar ratio. The solid line represents the best non-linear fit of the data to a 1:1 binding model (Ka = (1.15 ± 0.08) × 10^6 M⁻¹, ΔH = - 8.97 ± 0.076 kcal/mol, -TΔS = 0.703 kcal/mol).