Supporting Information

Cooperativity and Complexity in the Binding of Anions and Cations to a Tetratopic Ion-Pair Host

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1. Experimental

1.1 General materials and methods

Chemicals were purchased from Sigma-Aldrich, with the exceptions of tetrabutylammonium chloride from Merck and pyridine from Ajax Finechem. Anhydrous pyridine was purified by distillation and dried over potassium hydroxide. Anhydrous dichloromethane and tetrahydrofuran (HPLC grade from Honeywell Burdick & Jackson) were dried and deoxygenated using a PureSolv MD-7 solvent purification system (Innovative Technology, Inc., MA). Solvents used for chromatography were from Ajax Finechem and were purified by distillation. Column chromatography was performed using Davisil chromatographic silica media (0.040-0.063 mm). Thin layer chromatography was carried out using Merck Kieselgel 60 F-254 precoated sheets (0.25 mm). Deuterated solvents for NMR were purchased from Cambridge Isotope Laboratories.

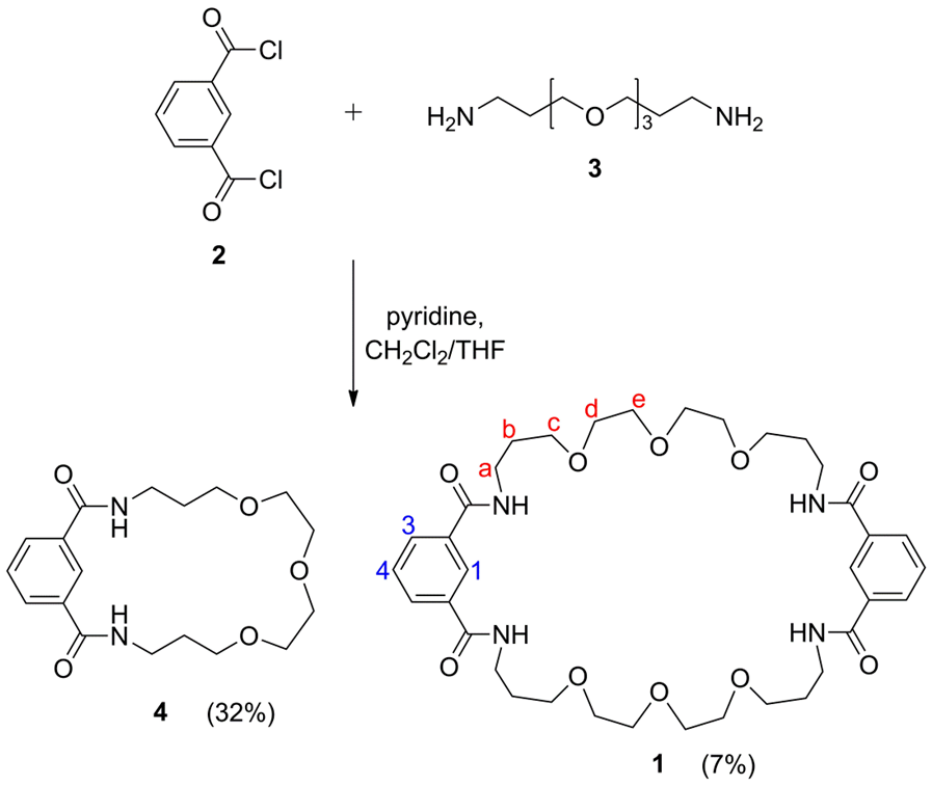
All synthetic reactions were carried out in an inert environment containing nitrogen. Melting points (mp) were determined on a Mel–Temp II hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 spectrometers operating at a frequency of 400.13 MHz for ^{1}H NMR and 100.61 for ^{13}C NMR respectively. NMR spectra were recorded at 298 K and samples were dissolved in the stated solvents and chemical shifts were referenced internally to residual solvent resonances. Signals are recorded in chemical shift (in ppm from residual solvent resonances referenced to tetramethylsilane, TMS), multiplicity, coupling constants (*J* in Hz), relative integral, and assignments in that order. Multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; quint, quintet; m, multiplet; dd, doublet of doublets; br t, broad triplet. ^{1}H assignments were made using 2–D NMR methods (COSY, HSQC, HMBC). NMR data were processed using standard Bruker software (TopSpin 3.1). Deuterated solvents were used as received except for deuterated chloroform, it was dried and deacidified by filtration through a plug of alumina and anhydrous potassium carbonate.

Low resolution electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass ZQ 2000 ESCi Multi-Mode Ionization Source mass spectrometer equipped with MassLynx 4.0 instrument software. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on a Thermo Scientific Linear Quadropole Ion Trap with Orbitrap Mass Analyser (LTQ ORBITRAP XL) mass spectrometer. Samples were acquired in electrospray ionization mode

using an in-house made static glass nanospray tips inserted onto an nanostage with 0.9 kV capillary voltage; FTMS setting at 60,000 resolution and the data then collected and processed with Xcalibur 2.0 instrument software. Elemental microanalysis was performed by the Research School of Chemistry, Australian National University, Canberra, Australia.

Scheme S1. Synthesis of the Ion-Pair Host **1**

1.2 Synthesis of bisisophthalamide-crown-6 (1) and characterization details



Scheme S1. Synthesis of the Ion-Pair Host **1**

Isophthaloyl dichloride **2** was prepared according to literature reference.[1]

A solution of isophthaloyl dichloride **2** (1.20 g, 5.91 mmol) in anhydrous tetrahydrofuran (30 mL) was added into a stirred solution of 4,7,10-trioxa-1,13-tridecanediamine **3** (2.00 g, 9.10 mmol) and anhydrous pyridine (0.978 g, 12.4 mmol), anhydrous tetrahydrofuran (50 mL) and anhydrous dichloromethane (50 mL) drop-wise over a period of 2 h, maintained at 0 ºC. After addition was completed, the reaction mixture was stirred for 16 h at room temperature to

afford an orange solution. The solvent was removed under reduced pressure, re-constituted in dichloromethane (50 mL) and washed with hydrochloric acid (0.1 M, 50 mL), followed by water (3 × 50 mL). The organic layer was concentrated in vacuo to afford the crude as a white solid residue. The crude product was purified by column chromatography over silica 60 with methanol in dichloromethane (5:95 v/v) to remove polymeric compounds and the eluent concentrated in vacuo. This fraction was then subject again to column chromatography over silica 60 with a gradient of methanol in dichloromethane (ranging from neat dichloromethane to 7:93 v/v). A less polar fraction (R_f = 0.26) and a more polar fraction (R_f = 0.18) were collected; TLC (methanol:dichloromethane, 5:95 v/v). The combined less polar fractions were concentrated to give the smaller macrocyclic isophthalamide-crown-3 **4** as a white solid (669 mg, 32%), The characterisation data is in good agreement with assignments based on previous reported synthesis via high pressure technique by Gryko *et al*.[2]

The combined more polar fractions were concentrated to yield the desired bisisophthalamide-crown-6 **1** as a white solid (141 mg, 7%), mp 128–130 ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 1.75 (quint, *J* = 6.5 Hz, 8H, H^b), 3.28-3.32 (m, 8H, H^a), 3.42-3.46 (m, 8H, H^c), 3.46-3.49 (m, 8H, H^d), 3.49-3.54 (m, 8H, H^e), 7.51 (t, *J* = 7.7 Hz, 2H, H^4), 7.91 (dd, *J* = 7.7, 1.7 Hz, 4H, $H^{3,5}$), 8.25 (t, *J* = 1.7 Hz, 2H, H^1), 8.49 (br t, *J* = 5.0 Hz, 4H, N*H*). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 29.3 (C^b), 36.8 (C^a), 68.3 (C^c), 69.6 (C^d), 69.8 (C^e), 126.0 (C^1), 128.3 (C^4), 129.6 ($C^{3,5}$), 134.8 ($C^{2,6}$), 165.8 (C=O). MS (ESI^+) *m/z*: 723.77 $[M + Na]^+$, requires 723.36. MS (ESI^-): *m/z* 699.38 $[M - H]^-$, requires 699.36). HRMS (ESI^+) *m/z*: $[M + H]^+$ calcd for $C_{36}H_{53}N_4O_{10}$: 701.3761, found: 701.3701; $[M + Na]^+$ calcd for $C_{36}H_{52}N_4O_{10}Na$: 723.3581, found: 723.3516. HRMS (ESI^-) *m/z*: $[M - H]^-$ calcd for $C_{36}H_{51}N_4O_{10}$: 699.3605, found: 699.3562; $[M + {}^{35}Cl]^-$ calcd for $C_{36}H_{51}N_4O_{10}{}^{35}Cl$: 735.3372, found: 735.3328; $[M + {}^{37}Cl]^-$ calcd for $C_{36}H_{51}N_4O_{10}{}^{37}Cl$: 737.3342, found: 737.3293.

Anal. Calcd (%) for $C_{36}H_{52}N_4O_{10}$: C, 61.70; H, 7.48; N, 7.99; O, 22.83. Found: C, 61.91; H, 7.21; N, 7.76; O, 23.12.

2. HRMS, ^{1}H and ^{13}C NMR Spectra of Host 1

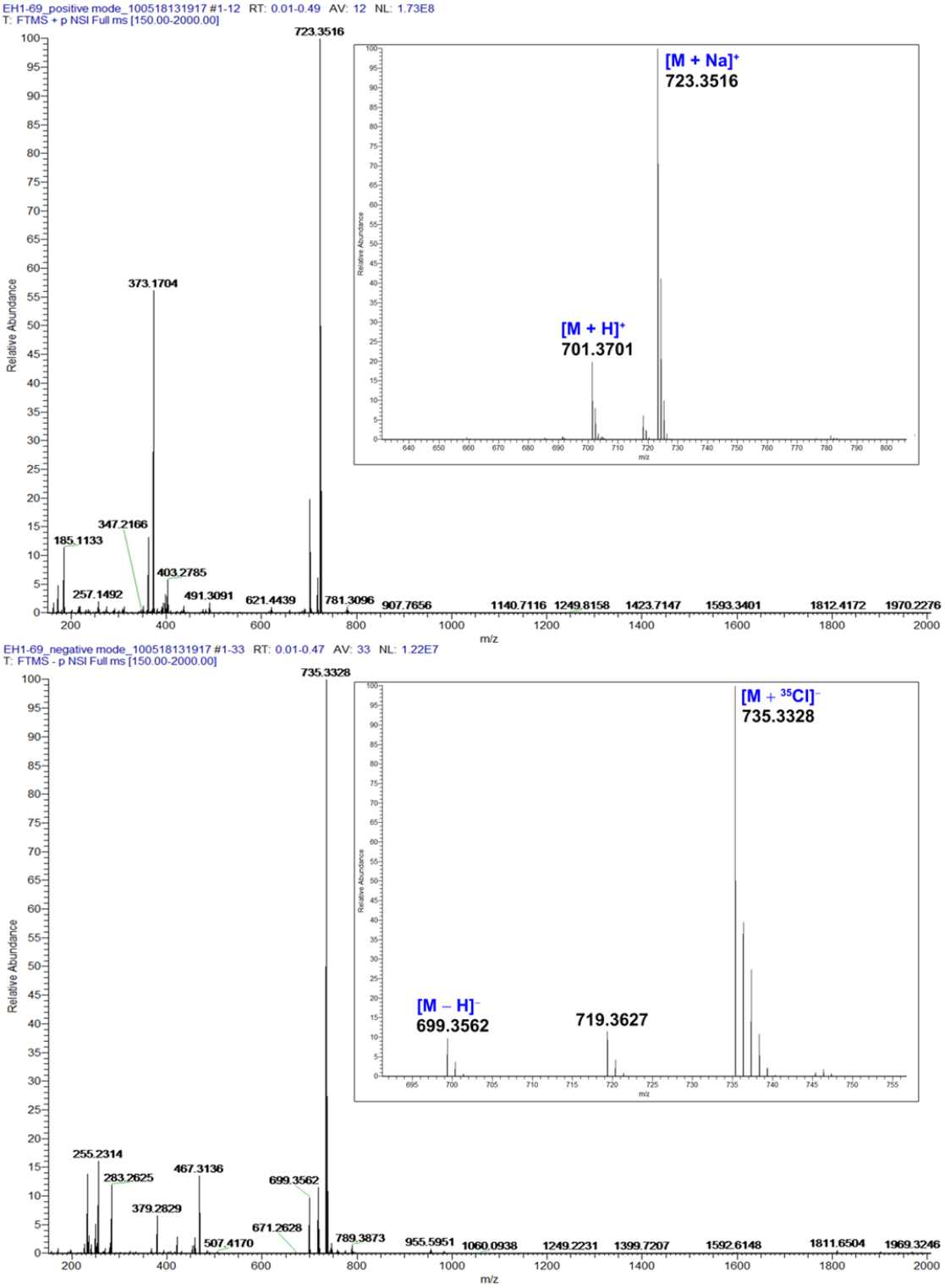


Figure S1. HR-ESI-MS (methanol) of host **1** showing adduct formation of [**1** + $Na]^{+}$ and [**1** + $^{35}Cl]^{-}$ at highest % abundance in the positive ESI^{+} (top) and negative ESI^{-} (bottom) respectively.

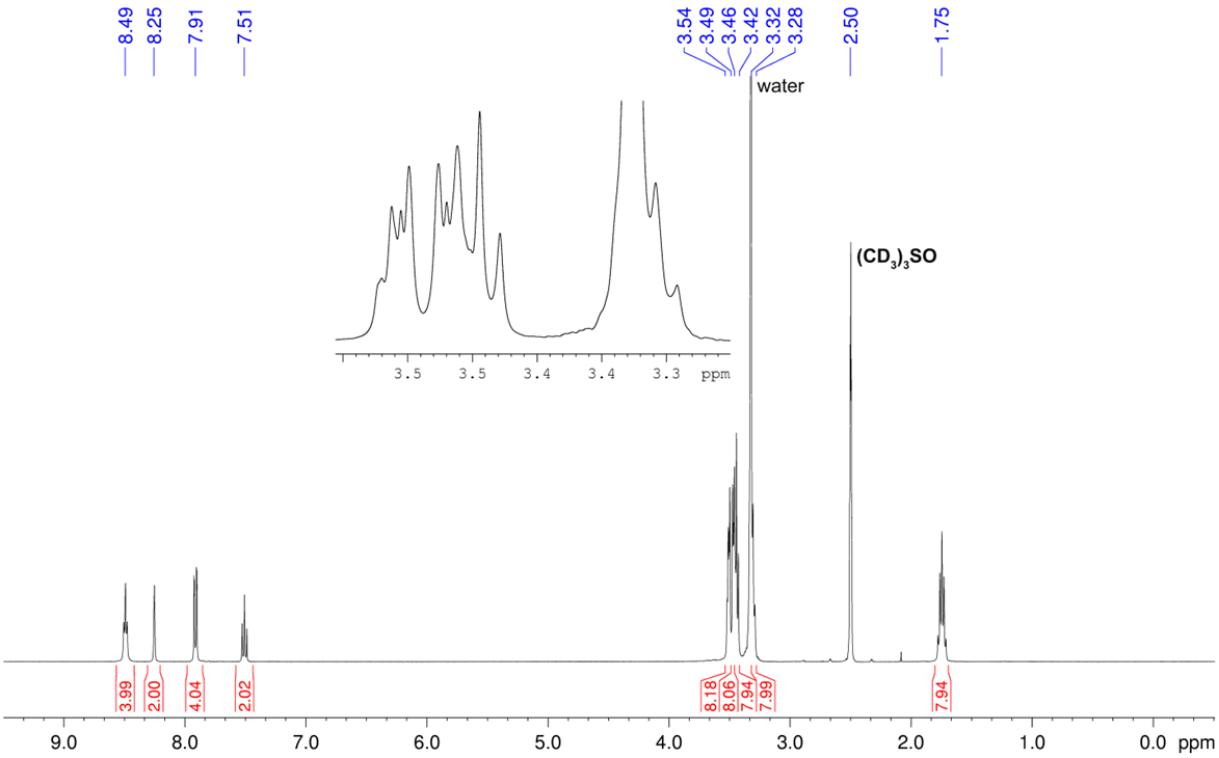


Figure S2. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) of host **1**.

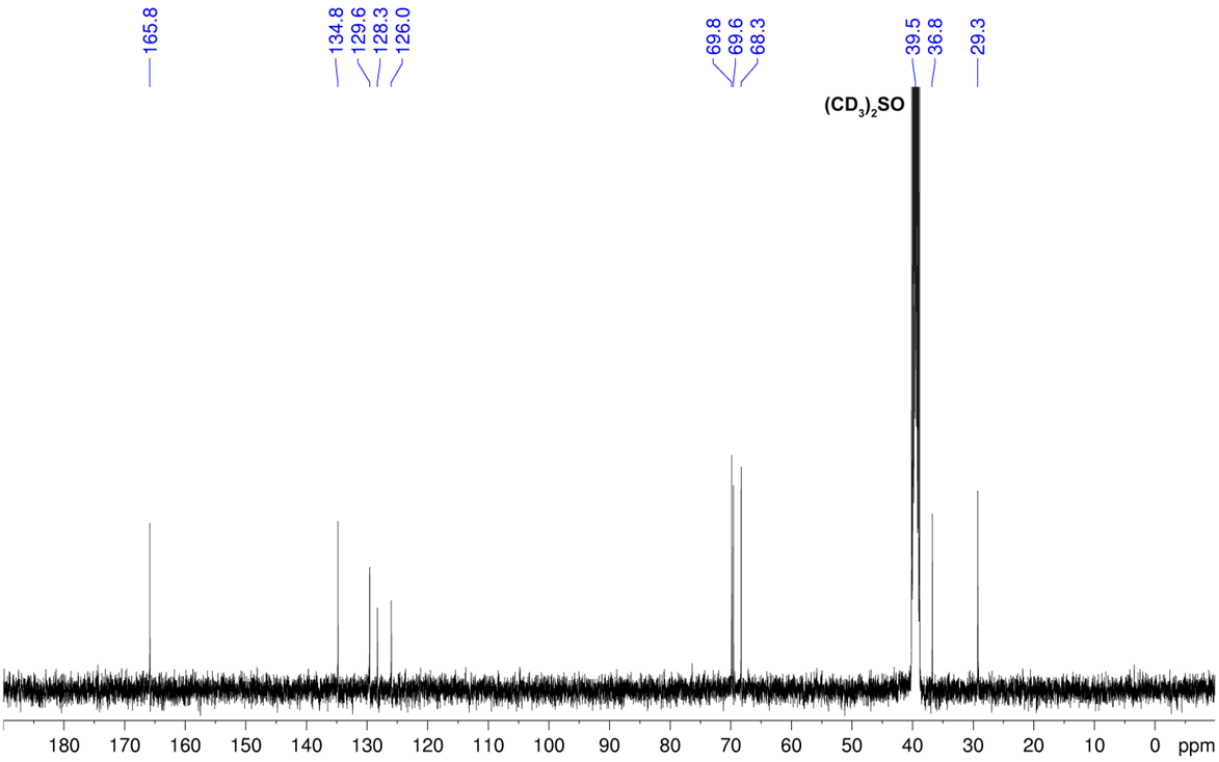


Figure S3. ^{13}C NMR (400 MHz, $(CD_3)_2SO$) of host **1**.

3. X-ray Crystallographic Structure Determination

The X-ray diffraction measurement for free host **1** and **1**•2[$Ca(ClO_4)_2$]•4H_2O complex were carried out using the Macromolecular Crystallography (MX) beamline at the Australian Synchrotron Facility, Melbourne using the Blu-Ice GUI controller software.[3] The crystal was mounted on the goniometer using the cryo-loop for diffraction intensity measurements, coated with paraffin oil and immediately transferred to the cold stream using the Oxford Cryostream 700 series low-temperature system. Data was collected using the Si<111> monochromatic synchrotron X-ray radiation at 100 K and was corrected for Lorentz and polarization effects using the XDS software.[4] The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement program SHELXL-97 and SHELXL-2013 to the final *R* value.[5, 6] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included by using a riding model. The conformational disordered atoms on the perchlorate anion and the macrocycle in the **1**•2[$Ca(ClO_4)_2$]•4H_2O complex were successfully modelled over two positions using the SADI and DELU restrain commands. The molecular graphics were generated using ORTEP-3[7] and Mercury[8] software packages. Further crystal and refinement data are given in Table S1.

Crystallographic data have been deposited at the CCDC and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223–336–033; or email: deposit@ccdc.cam.ac.uk.

Table S1. Summary of crystallographic and refinement data for free host 1 and for the 1•2[Ca(ClO$_4$)$_2$]•4H$_2$O complex

Structure	Free host **1**	**1**•2[Ca(ClO$_4$)$_2$]•4H$_2$O complex
CCDC number	994170	994171
Empirical formula	$C_{36}H_{52}N_4O_{10}$	Ca_2•$C_{36}H_{60}N_4O_{14}$•4(ClO_4)
Formula weight	700.82	1250.84
Crystal form	Colorless thin plates	Colorless thin plates
Crystal size/mm^3	0.10 × 0.02 × 0.02	0.02 × 0.02 × 0.01
Temperature/K	100 (2)	100 (2)
Radiation Type	Synchrotron (λ = 0.71085 Å)	Synchrotron (λ = 0.71073 Å)
Crystal system	Orthorhombic	Triclinic
Space group	*Pccn*	$P\bar{1}$
a/Å	14.429 (3)	8.2180 (16)
b/Å	28.690 (6)	9.6910 (19)
c/Å	8.5200 (17)	18.377 (4)
α/°	90.00	101.24 (3)
β/°	90.00	92.31 (3)
γ/°	90.00	110.51 (3)
Volume/Å^3	3527.0 (12)	1335.0 (5)
Cell formula unit, *Z*	4	2
Calculated density, D_c/g cm^{-3}	1.320	1.556
Absorption coefficient, μ/mm^{-1}	0.10	0.51
F(000)	1504	652
θ range for data collection/°	2.5–22.5	2.5–22.5
Reflections collected	42040	16914
Independent reflections	3071 [R_{int} = 0.164]	4367 [R_{int} = 0.051]
Observed reflections with [$I > 2\sigma(I)$]	2792	3556
Parameters / Restraints	226 / 0	354 / 41
Largest diff. peak and hole $\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	0.28 and –0.32	1.47 and –1.53
Goodness-of-fit on F^2	1.064	1.031
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0519; wR_2 = 0.1323	R_1 = 0.0766; wR_2 = 0.1918
R indices (all data)	R_1 = 0.0551; wR_2 = 0.1354	R_1 = 0.0914; wR_2 = 0.2033

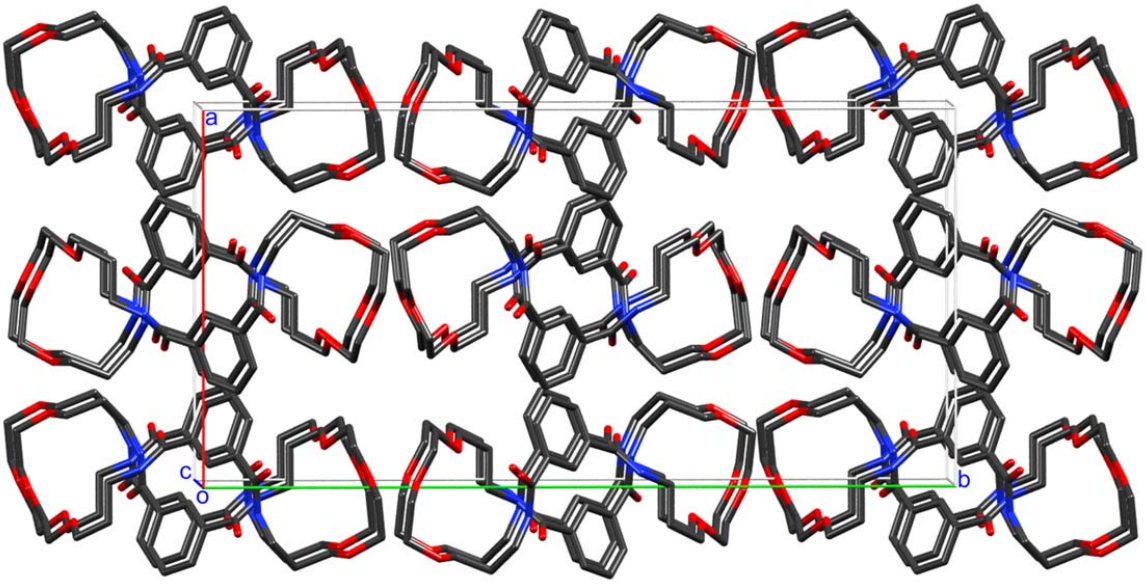


Figure S4. Crystallographic packed diagram of host **1** with the unit cell viewed down the *c* axis, all H atoms are omitted for clarity. This figures illustrating the packing of host **1** without the presence of guest inclusion and co-crystallizing solvents.

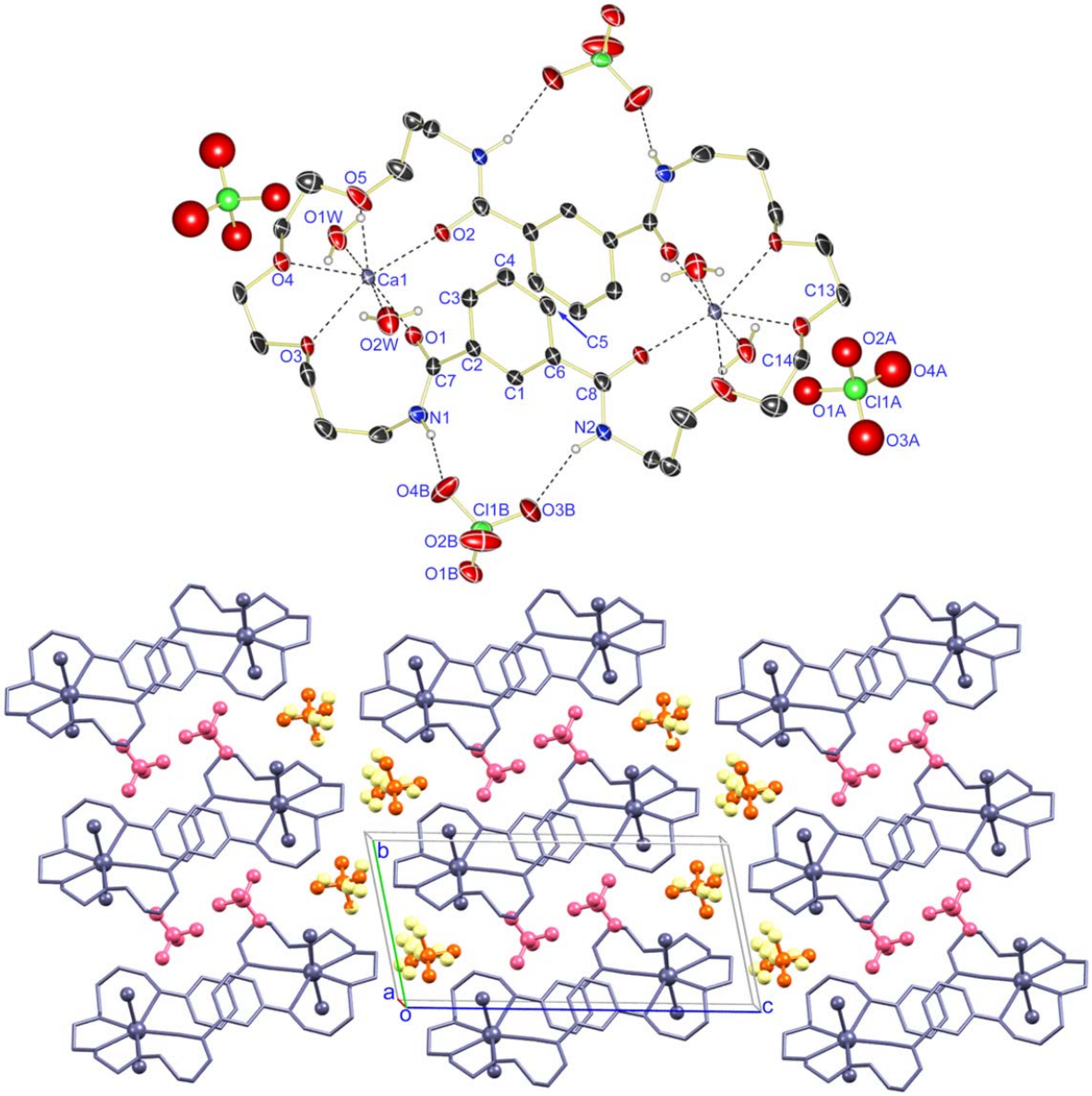


Figure S5. Molecular structure of **1**•2[$Ca(ClO_4)_2$]•4H_2O H:G complex derived from the single crystal X-ray analysis. (Top) ORTEP diagram showing 50% probability anisotropic displacement ellipsoids at 100(2) K, all H atoms are omitted for clarity, except amide-H and H_2O. The unbound ClO_4^- atoms (ball and stick) are disordered over two positions with an occupancy ratio of 0.7:0.3; and two proximal carbon atoms (C13, C14) are disordered over two equally occupied sites; only the major orientation is shown. (Bottom) Crystallographic packed diagram with the unit cell viewed down the *a* axis, all H atoms are omitted for clarity. Atoms are colour-coded in symmetry equivalence.

4. Methodology for ^{1}H NMR Titration Binding Studies and Binding Models

NMR titrations were conducted in triplicate or quadruplicate repeats on a Bruker Avance III 400 spectrometer operating at a frequency of 400.13 MHz with the probe temperature maintained at 298 K. In all cases, NMR titrations were performed maintaining the concentration (usually around 1.0 mM) of the host constant by dissolving the guest in the same host solution, followed by addition of that guest dissolved in the host solution to the NMR sample of the host (+ any previously added guest in host solution or other additives), delivered accurately using 25 or 100 μL Hamilton Microlitre syringes. After each addition, the samples were shaken thoroughly within the air-tight screw-cap NMR sample tubes and then allowed to equilibrate in the NMR probe for 1 min before the spectra were recorded.

Host **1** and all salts were dried under high vacuum for 24 h before use; all anions were added as tetrabutylammonium (TBA^+) salts. For cations, Na^+ was added as perchlorate salt ($NaClO_4$), K^+ as hexafluorophosphate salt (KPF_6), Mg^{2+} as diperchlorate salt ($Mg(ClO_4)_2$) and Ca^{2+} as diperchlorate tetrahydrate salt ($Ca(ClO_4)_2 \bullet 4H_2O$). Four different deuterated solvent mixtures of the following were used to study the effect of solvents on the binding of anions and cations towards host **1**; DMSO-d_6/acetone-d_6 (1:9, v/v), $CDCl_3/CD_3CN$ (1:9, v/v), $CDCl_3/CD_3CN$ (1:1, v/v) and $CDCl_3/CD_3OD$ (9:1, v/v). Stock solutions of host **1** (1.0 mM) were prepared in the four different solvent mixtures by weighing for better accuracy. When necessary for cooperativity studies with the co-presence of Ca^{2+}, $Ca(ClO_4)_2$ was added in one or five mole equivalents to the host in the preparation of the stock solutions. These stock solutions (weighed) were then used for the preparation of the titrating standard solutions containing approximately 20-200 mM of the guest anion or cation salts, hence maintaining the concentration of host **1** around 1.0 mM.

Typically, to approximately 600 μL (weighed) of a stock solution of host **1** (1.0 mM), were added small aliquots (1-100 μL) of a standard solution. For each titration, 15-30 data points were collected, and approximately 10-100 equivalents of the ionic salt guest present at the end of the titration, dependent on the amount of guest species required for the binding towards the host to attain saturation.

In all cases of ^{1}H NMR titration binding studies, all proton resonances were monitored to study the trends of the change in chemical shifts. Thenceforth, two to four different proton resonances

were recorded, providing multiple sets of data from which the association constants can be determined by fitting to binding models using a custom written program *fittingprogram*[9] developed by A/Prof. Pall Thordarson within the Matlab[10] platform. The full set of scripts used in *fittingprogram* has been previously published.[11] The program uses the non-linear regression function *fminsearch* in Matlab with the Simplex algorithm[12] and the global analysis[13] method for the multiple data sets in the iteration process to optimize the results for association constants and other unknown parameters.

It should be emphasized that the global analysis approach, fitting all data sets simultaneously, greatly enhances the quality of the fitting procedure.[14] The data was fitted to 1:1, 1:2 and 2:1 equilibria, with up to six different binding models (H = host, G = guest, $[X]_0$ total concentration of species X, and K = association constants) as discussed further in below.

Full details on the equations and terminology used here for the binding models used have been published previously.[9] Below the most important equations referred to in this paper are summarized:

The association constants can also be known as the equilibrium constants (K_a) for the simple 1:1 H:G complexation as according to equation (S1) can be expressed in free energy (ΔG_a) according to equation (S2).[9]

$$K_a = \frac{[HG]}{[H][G]} \qquad \text{Eq. (S1)} \qquad\qquad \Delta G_a = -R\mathrm{T}\ln K_a \qquad \text{Eq. (S2)}$$

For 1:2 H:G_2 complexation as according to equation (S3) and (S4), the stepwise association constants (K_1 and K_2) can be expressed in terms of the free energy changes (ΔG_1 and ΔG_1) according to equations (S6) and (S7)[9] using the microscopic stepwise association constants (K_{1m} and K_{2m}) which are derived from the stepwise association constants as $K_{1m} = K_1/2$ and $K_{2m} = 2K_2$.

$$K_1 = \frac{[HG]}{[H][G]} \quad \text{Eq. (S3)} \qquad K_2 = \frac{[HG_2]}{[HG][G]} \quad \text{Eq. (S4)} \qquad \beta_{12} = K_1K_2 \quad \text{Eq. (S5)}$$

$$\Delta G_1 = -R\mathrm{T}\ln K_{1m} = -R\mathrm{T}\ln\left(\frac{K_1}{2}\right) \quad \text{Eq. (S6)}$$

$$\Delta G_2 = -R\mathrm{T}\ln K_{2\mathrm{m}} = -R\mathrm{T}\ln(2K_2) \quad \text{Eq. (S7)}$$

The interaction parameter (α)[15] for the stepwise formation of a 1:2 homotropic H:G_2 complex according to equation (S8) provides an insight for the cooperativity effect between the formation of 1:1 and 1:2 complexes.[16] If α = 1 (i.e. $K_{1\mathrm{m}} = K_{2\mathrm{m}}$), the stepwise 1:2 binding is non-cooperative; if α > 1 (i.e. $K_{1\mathrm{m}} < K_{2\mathrm{m}}$), the stepwise 1:2 binding is positively cooperative; if α > 1 (i.e. $K_{1\mathrm{m}} < K_{2\mathrm{m}}$) the stepwise 1:2 binding is negatively cooperative.[17]

$$\alpha = \frac{K_1}{4K_2} = \frac{K_{1\mathrm{m}}}{K_{2\mathrm{m}}} \quad \text{Eq. (S8)}$$

Binding models:

In the data below five different binding models are usually compared.

1. The first on is classical **1:1** equilibria. Here, we define the NMR resonance for the host as δ_H, the guest as δ_G and the host-guest complex as δ_{HG}. From this, we can also define the change in resonance for the host-guest complexation as $\delta_{\Delta HG} = \delta_{HG} - \delta_H$. If we then define δ_0 = NMR resonance of the host before the guest is added (before the start of titration) we can define the change in in resonance as $\Delta\delta = \delta - \delta_0$. We can now write the NMR version of our simple 1:1 equilibria according to equation (S9) which is derived from the generic quadratic equation used to calculate the concentration of host-guest complex [HG] as previously described.[9]

$$\Delta\delta = \frac{\delta_{\Delta HG}}{[H]_0}\left(\frac{1}{2}\left\{\left([G]_0 + [H]_0 + \frac{1}{K_a}\right) - \sqrt{\left([G]_0 + [H]_0 + \frac{1}{K_a}\right)^2 + 4[H]_0[G]_0}\right\}\right) \quad \text{Eq. (S9)}$$

2. The second one is the stepwise (non-degenerate) "**full 1:2**" binding model. This model assumes two non-identical two binding sites per molecule of host **1** that allows for cooperativity (negative or positive). As with the 1:1 equilibria we first define $\delta_{\Delta HG_2}$ as the difference between in NMR resonance between the 1:2 host-guest complex (δ_{HG_2}) and the host NMR resonance (δ_H), that is $\delta_{\Delta HG_2} = \delta_{HG_2} - \delta_H$. Using $\delta_{\Delta HG} = \delta_{HG} - \delta_H$ for the change in NMR resonance for the 1:1

complex formation and the observed change in resonance as $\Delta\delta = \delta - \delta_0$ as before with the 1:1 equilibria, we obtain equation (S10).

$$\Delta\delta = \frac{\delta_{\Delta HG} K_1[G] + \delta_{\Delta HG_2} K_1 K_2 [G]^2}{1 + K_1[G] + K_1 K_2 [G]^2} \quad \text{Eq. (S10)}$$

Here the guest [G] concentration is obtained from the cubic equation (S11).[11]

$$[G]^3 (K_1 K_2) + [G]^2 \{K_1 (2K_2[H]_0 - K_2[G]_0 + 1)\} + [G]\{K_1([H]_0 - [G]_0) + 1\} - [G]_0 = 0 \quad \text{Eq. (S11)}$$

Notably, for the "**full 1:2**" model we make no assumptions about the correlation between either K_1 and K_2 ($K_1 \neq 4K_2$) or $\delta_{\Delta HG_2}$and $\delta_{\Delta HG}$ ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$).

3. The third one is the stepwise (non-degenerate) "**additive 1:2**" binding model. To reduce the number of fitted parameters we note that in many circumstances it can be assumed that the induced chemical shifts of the protons being monitored in the NMR experiment are simply additive, i.e. for proton resonance Y, the shift caused by the second binding event is exactly the same as from the first binding. It then follows that $\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$ and we can simplify equation (S10) to yield equation (S12).

$$\Delta\delta = \frac{\delta_{\Delta HG} K_1[G](1 + 2K_2[G])}{1 + K_1[G] + K_1 K_2 [G]^2} \quad \text{Eq. (S12)}$$

We have for the "**additive 1:2**" model therefore made the assumption that $\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$, whilst not making any assumptions about the correlation between either K_1 and K_2 ($K_1 \neq 4K_2$).

4. The forth model is the stepwise "**non-coopeartive 1:2**" model. Here we revert back to noting that the chemical shift differences between the first and second binding may not be correlated ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$) but instead we make the assumption that the 1:2 binding is non-coopeartive and therefore that $K_1 = 4K_2$. It is then easy to see from equation (S5) that the overall 1:2 binding constant $\beta_{12} = K_1/4 \times 4K_2$ and hence, $K_1 = 2\sqrt{\beta_{12}}$ and $K_2 = (\sqrt{\beta_{12}})/2$. We can then use this to rewrite equation (S10) and replace K_1 and K_2 with a single parameter β_{12} to obtain equation (S13). If desired, K_1 and K_2 can then be calculated back from β_{12}.

$$\Delta\delta = \frac{\delta_{\Delta HG}\, 2\sqrt{\beta_{12}}[G] + \delta_{\Delta HG_2}\beta_{12}[G]^2}{1 + 2\sqrt{\beta_{12}}[G] + \beta_{12}[G]^2} \quad \text{Eq. (S13)}$$

We have in "**non-cooperative 1:2**" model made the assumption that $K_1 = 4K_2$ whilst making no assumption about the correlation between $\delta_{\Delta HG_2}$and $\delta_{\Delta HG}$ ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$).

5. The fifth model is the "**statistical 1:2**" model. Here we not only make the assumption that the binding is non-cooperative ($K_1 = 4K_2$) but also that the chemical shift changes are simply additive $\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$. This means in other words we make the assumption that the two binding site behave like two independent hosts. This leads to a further simplification of equation (S10) to equation (S14).

$$\Delta\delta = \frac{\delta_{\Delta HG} K_1[G](1 + 2K_2[G])}{1 + K_1[G] + K_1K_2[G]^2} \quad \text{Eq. (S14)}$$

In this "**statistical 1:2**" model we have therefore made the assumptions that $K_1 = 4K_2$ and that $\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$. It should also be noted that in this situation, the data could also be fitted to the simple **1:1** model according to Equation (S9) by simply multiply the total host concentration $[H]_0$ by a factor of 2. The resulting association constant K_a is then equal to the non-coopeartive microscopic binding constants, i.e. $K_a = K_{1m} = K_{2m}$, which means $K_1 = K_a/2$ and $K_2 = 2K_a$.

For the 2:1 H_2:G equilibrium, all the above mentioned 1:2 binding models can be used in a similar fitting process, simply by defining the guest species as [H] and the host as [G] in the binding models.[9]

As important it as to determine which overall binding equilibria (i.e. 1:1, 1:2 or 2:1) fits best to the NMR titration data for the host-guest complexation of host **1**, it is also essential to consider the most suitable variant of binding model for the more complex 1:2 equilibria describes the system appropriately. This involves taking into consideration various factors concerning the quality of non-linear regression curve fit for these different binding models to the original data versus the number of unknown parameters used in the fitting process.

Firstly, the plots of the experimental data (plotted as points) along with the calculated data (plotted as line) were examined (refer to figures below for examples), in conjunction with the inspection of the scatter diagram residual plots. These data residuals can be computed to provide quantitative analysis for the quality of the fit (i.e. goodness of fit indices)[18] to compare the between different binding models. Herein, the chi-squared (χ^2) and covariance of the fit (cov_{fit}) indices are both used to assess the quality of the fit; the lower the value of the index, the better the fit. It is useful to look at more than one goodness of fit value when comparing different binding models for a more robust conclusion. The chi-squared (χ^2) value is defined according to equation (S16), taking the sum of the squared of residuals, corrected with the number of data points (N) and the number of parameters used (k).[19]

$$\chi^2 = \sqrt{\frac{\sum\left(\Delta\delta_{data} - \Delta\delta_{calc}\right)^2}{N-k-1}} \quad \text{Eq. (S16)}$$

The covariance of the fit (cov_{fit}) is calculated by dividing the (co)variance of the residual (experimental data – calculated data) with the covariance of the experimental data.[11] This value is independent of the number of parameters but reflects the distributions of the residuals. Since there are triplicate or quadruplicate repeated measurements, the average cov_{fit} factor is calculated by dividing the cov_{fit} from fitting to 1:1 binding model with cov_{fit} from each 1:2 binding models for each individual measurement repeats, and averaged from the number of repeats; thus providing a better overall comparison of the cov_{fit}. Due to the higher number of parameters in the full, additive and non-cooperative 1:2 binding models, it is important to have a significant improvement in the cov_{fit} (> 2-3 fold) when comparing the respective 1:2 models to the 1:1 model before concluding the best binding model for the titration experimental raw data.

It is also equally important to review if the results of the fitted parameters are logical. For example, the association constants, K cannot be negative and for K much larger than 10^5 M^{-1} should be regarded unreliable for NMR titration measurements. Likewise, the estimated change in chemical shifts (i.e. $\delta_{\Delta HG_2}$and $\delta_{\Delta HG}$) should be within a sensible range. The estimation of uncertainty in these experiments is based on the 95% confidence interval which is calculated as: standard deviation of the mean (std/$\sqrt{n}$) multiplied by the inverse student t-value at the 0.05 level and the appropriate degrees of freedom (n – 1) with n = number of experiments.[20]

To summarize, the key difference between the above binding models is how many parameters are fitted in the fitting progress which can be conveniently noted as number of parameters = (*n*-*df*), where *n* = number of data points in the fit and *df* = degrees of freedom. In the below examples, the up to six different binding models that were compared are (see also Table 1 in the main article):

Table S2. Key features and differences of the binding models compared in this work.

Name	No. of fitted Parameters (*n*-*df*)	Stoichiometry (host:guest)	Relationship between	
			K_1 and K_2	$\delta_{\Delta HG}$.and $\delta_{\Delta HG_2}$
1:1	1 + 1 × H-studied[a]	1:1	N/A	N/A
Full 1:2	2 + 2 × H-studied[a]	1:2	$K_1 \neq 4K_2$	$\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$
Full 2:1	2 + 2 × H-studied[a]	2:1	$K_1 \neq 4K_2$	$\delta_{\Delta H_2G} \neq 2\delta_{\Delta HG}$
Additive 1:2	2 + 1 × H-studied[a]	1:2	$K_1 \neq 4K_2$	$\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$
Non-cooperative 1:2	1 + 2 × H-studied[a]	1:2	$K_1 = 4K_2$	$\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$
Statistical 1:2	1 + 1 × H-studied[a]	1:2	$K_1 = 4K_2$	$\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$

[a]H-studied means how many proton resonances are used in the global fit. E.g. if two different proton resonances such as N-H and Ar-H are used, H-studied = 2 and total number of parameters fitted (*n*-*df*) in the **full 1:2** model (*n*-*df*) = 6 but (*n*-*df*) = 4 in the **additive 1:2** model.

When comparing results from different binding model is therefore important not only to look at the quality of fit but also how many parameters (*n*-*df*) were used in the fitting process (as the fit should get better with increasing number of parameters). The information about the number of parameters (*n*-*df*) is therefore included in the Tables below. In most circumstances one model clearly stands out as giving the best fit regardless of the number of parameters (*n*-*df*) and this model will of focus in the main article.

However, in some instances it is impossible to pinpoint one model that is clearly better than all the others – in those circumstances both (or all three on rare occasions) will be discussed in the main article.

5. Data Analysis for Anion Binding Studies

In all cases of anion binding studies for host **1**, two different proton resonances (amide-H and aromatic-H1) were recorded at every titration point, providing two sets of data for the binding models fitting analysis. Herein, the results from fitting to the **1:1**, **full 1:2** and **additive 1:2** binding models are reported for three different solvent mixtures; DMSO-d_6/acetone-d_6 (1:9, v/v), $CDCl_3/CD_3CN$ (1:9, v/v) and $CDCl_3/CD_3CN$ (1:1, v/v). In the fourth solvent mixture, $CDCl_3/CD_3OD$ (9:1, v/v), the titration of anion salts did not induce significant $\Delta\delta$ (< 0.05 ppm), thus no binding model fitting analysis was performed. The **non-cooperative 1:2** and **statistical 1:2** are excluded from the analysis below as attempted to fit the data to these fairly simple model actually resulted in *worse* fit (based on cov_{fit}) than that obtained by the simple **1:1** model.

Table S3. Association constants of host 1 towards the acetate anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-acetate in DMSO-d_6/acetone-d_6 (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	1.07	1	5440	-	-	–21.3	-
	2	2.23	1	3670	-	-	–20.3	-
	3	2.46	1	4890	-	-	–21.0	-
	Avg. (S.D.)	**1.92 (0.75)**	**1**	**4670 (910)**	-	-	**–20.9 (0.5)**	-
	95% C.I.	1.86	0	2250 (48%)	-	-	1.3	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.13	8.2	10200	11.4	116	–21.2	–7.74
	2	0.19	12	8310	36.2	301	–20.6	–10.6
	3	0.79	3.1	10500	7.27	76.2	–21.2	–6.63
	Avg. (S.D.)	**0.37 (0.36)**	**7.7**	**9660 (1180)**	**18.3 (15.6)**	**164 (120)**	**–21.0 (0.3)**	**–8.33 (2.05)**
	95% C.I.	0.90	8.0	2930 (30%)	38.8 (212%)	297	0.8	5.09
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.16	6.7	10700	27.0	289	–21.3	–9.89
	2	0.21	11	7940	25.2	200	–20.5	–9.71
	3	0.82	3.0	11400	30.1	344	–21.4	–10.2
	Avg. (S.D.)	**0.39 (0.37)**	**6.8**	**10000 (1830)**	**27.4 (2.5)**	**277 (73)**	**–21.1 (0.5)**	**–9.92 (0.22)**
	95% C.I.	0.91	7.0	4550 (45%)	6.2 (23%)	180	1.2	0.56

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

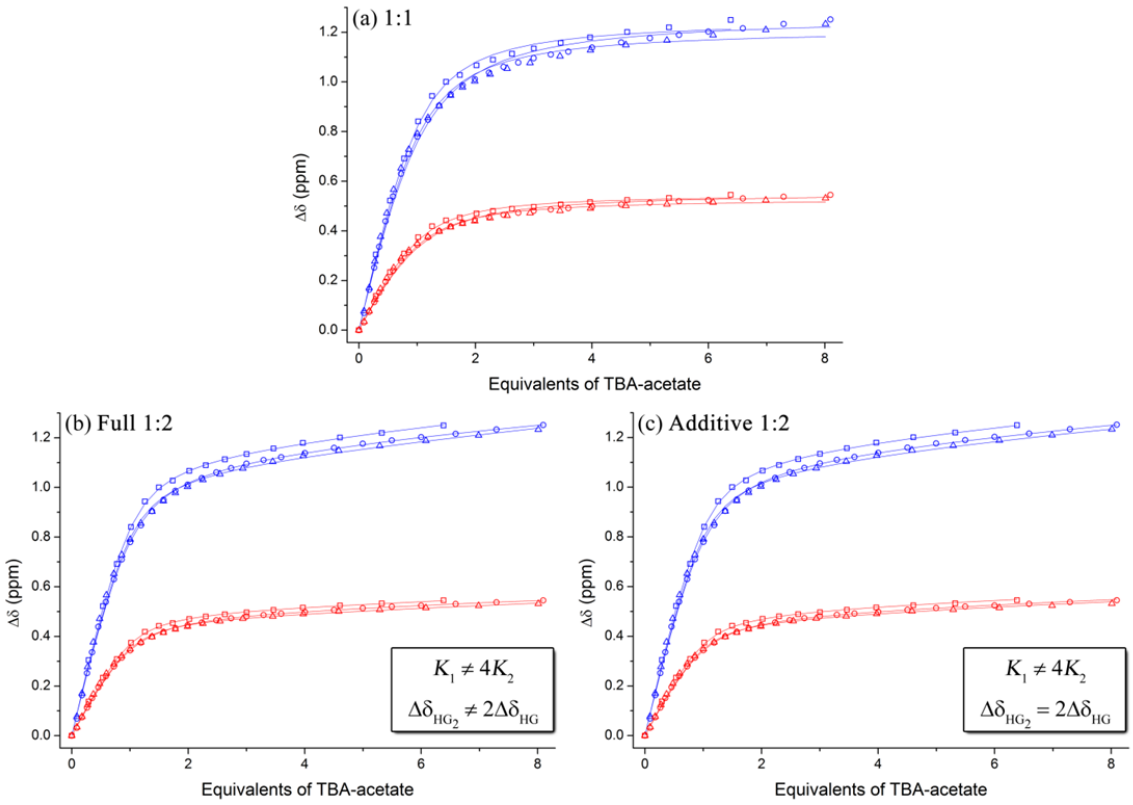


Figure S6. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-acetate in DMSO-d_6/acetone-d_6 (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** and **additive 1:2** are very similar in cov_{fit} but always much better than **1:1**. Given the small difference in cov_{fit} between the two former ones and the differences in (n-df), both the **full 1:2** and **additive 1:2** binding model need to be considered.

Table S4. Association constants of host 1 towards the chloride anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-Cl in DMSO-d_6/acetone-d_6 (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	5.09	1	2300	-	-	–19.2	-
	2	6.09	1	1780	-	-	–18.5	-
	3	8.54	1	2080	-	-	–18.9	-
	Avg. (S.D.)	**6.57 (1.77)**	**1**	**2050 (260)**	-	-	**–18.9 (0.3)**	-
	95% C.I.	4.41	0	640 (31%)	-	-	0.8	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.75	6.8	5360	47.9	257	–19.6	–11.3
	2	0.11	55	4200	30.4	128	–19.0	–10.2
	3	0.26	33	5700	43.5	248	–19.7	–11.1
	Avg. (S.D.)	**0.37 (0.34)**	**32**	**5090 (790)**	**40.6 (9.1)**	**211 (72)**	**–19.4 (0.4)**	**–10.8 (0.6)**
	95% C.I.	0.84	45	1960 (38%)	22.6 (56%)	179	1.0	1.5
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.80	6.4	4600	19.6	90.3	–19.2	–9.09
	2	0.21	29	3920	19.2	75.1	–18.8	–9.04
	3	0.43	20	4950	21.9	108	–19.4	–9.36
	Avg. (S.D.)	**0.48 (0.30)**	**18**	**4490 (530)**	**20.2 (1.4)**	**91.2 (16.5)**	**–19.1 (0.3)**	**–9.16 (0.17)**
	95% C.I.	0.74	21	1310 (29%)	3.6 (18%)	41.1	0.7	0.43

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

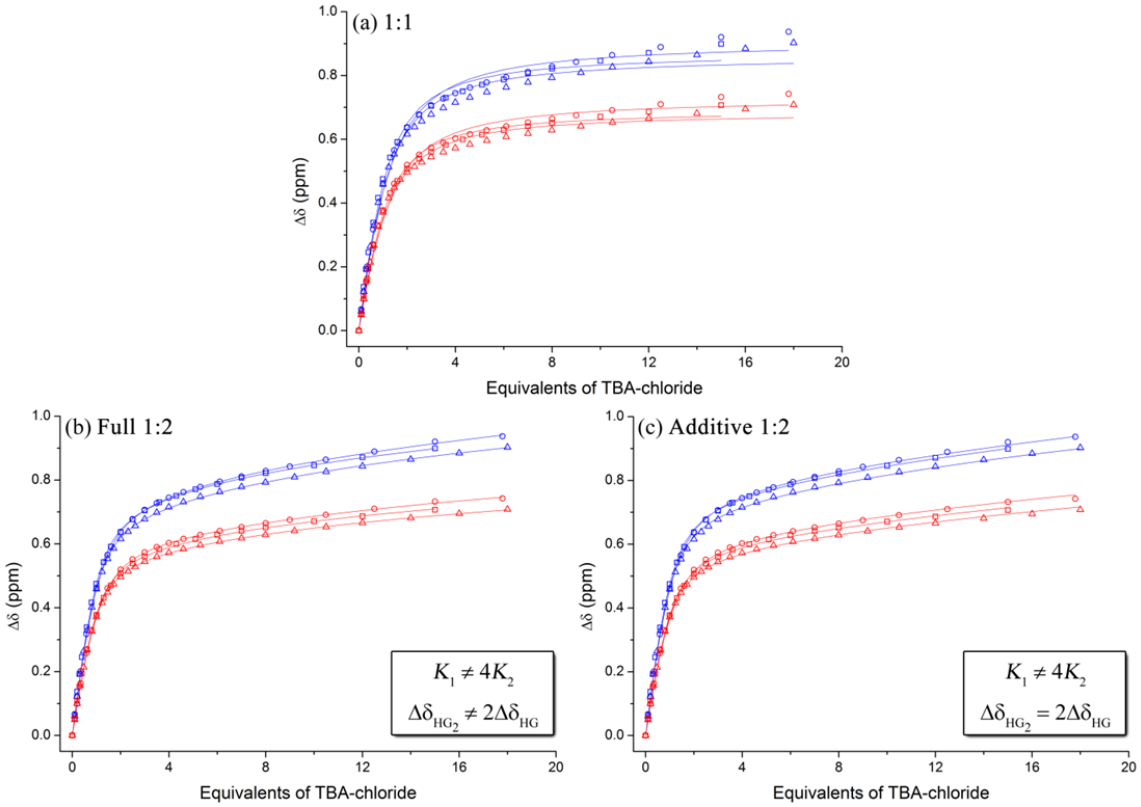


Figure S7. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-chloride in DMSO-d_6/acetone-d_6 (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2.**

Conclusion: The **full 1:2** and **additive 1:2** are similar in cov_{fit} but always much better than **1:1**. Given the small difference in cov_{fit} between the two former ones and the differences in (n-df), both the **full 1:2** and **additive 1:2** binding model need to be considered.

Table S5. Association constants of host 1 towards bromide anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-Br in DMSO-d_6/acetone-d_6 (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	4.41	1	295	-	-	–14.1	-
	2	3.25	1	272	-	-	–13.9	-
	3	3.82	1	271	-	-	–13.9	-
	Avg. (S.D.)	**3.83 (0.58)**	**1**	**279 (14)**	-	-	**–14.0 (0.1)**	-
	95% C.I.	1.4	0	34 (12%)	-	-	0.3	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.11	40	966	50.5	48.8	–15.3	–11.4
	2	0.05	65	670	38.4	25.7	–14.4	–10.8
	3	0.11	35	864	53.9	46.5	–15.0	–11.6
	Avg. (S.D.)	**0.09 (0.03)**	**47**	**834 (151)**	**47.6 (8.1)**	**40.4 (12.7)**	**–14.9 (0.5)**	**–11.3 (0.4)**
	95% C.I.	0.08	30	374 (45%)	20.2 (42%)	31.6	1.2	1.1
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.33	13	657	35.1	23.0	–14.6	–10.5
	2	0.12	27	610	33.4	20.4	–14.2	–10.4
	3	0.27	14	663	37.8	25.0	–14.4	–10.7
	Avg. (S.D.)	**0.24 (0.11)**	**18**	**643 (29)**	**35.4 (2.2)**	**22.8 (2.3)**	**–14.3 (0.1)**	**–10.6 (0.2)**
	95% C.I.	0.27	14	72 (11%)	5.5 (16%)	5.8	0.3	0.4

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

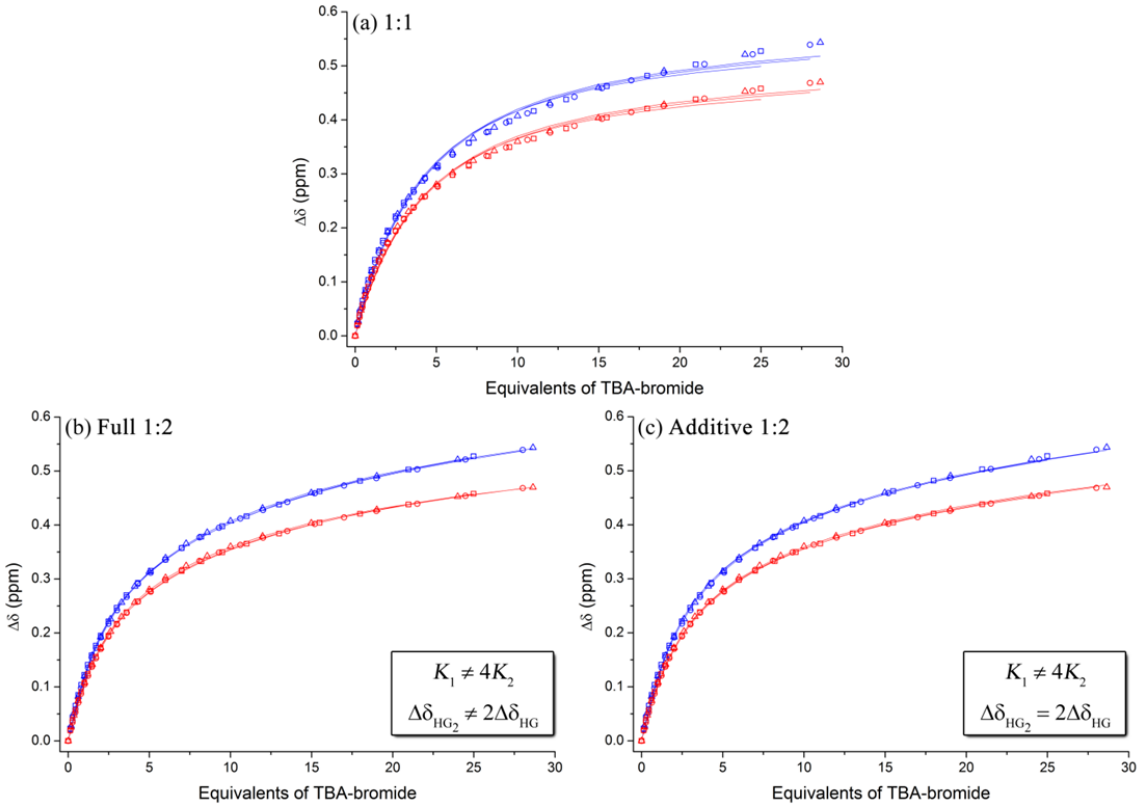


Figure S8. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-bromide in DMSO-d_6/acetone-d_6 (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** and **additive 1:2** are a bit different in cov_{fit}, with former always considerably better but both much better than **1:1**. Given though the smaller (n-df) for the **additive 1:2** model, it is difficult to rule it inferior to the **full 1:2** despite of the difference in cov_{fit} between those two, hence both the **full 1:2** and **additive 1:2** binding model need to be considered.

Table S6. Association constants of host 1 towards the iodide anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-I in DMSO-d_6/acetone-d_6 (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	4.42	1	26.3	-	-	–8.10	-
	2	4.01	1	27.9	-	-	–8.25	-
	3	1.78	1	26.1	-	-	–8.08	-
	Avg. (S.D.)	**3.40 (1.42)**	**1**	**26.8 (1.0)**	-	-	**–8.14 (0.09)**	-
	95% C.I.	3.53	1	2.5 (9%)	-	-	0.23	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.10	44	211	10.5	2220	–11.5	–7.55
	2	0.10	40	200	11.3	2260	–11.4	–7.73
	3	0.05	36	116	10.8	1250	–10.1	–7.61
	Avg. (S.D.)	**0.08 (0.03)**	**40**	**176 (52)**	**10.9 (0.4)**	**1910 (580)**	**–11.0 (0.8)**	**–7.63 (0.09)**
	95% C.I.	0.06	8	130 (74%)	1.0 (9%)	1430	2.1	0.22
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	2.41	1.8	45.0	4.45	200	–7.71	–5.42
	2	1.65	2.4	48.6	4.55	221	–7.91	–5.47
	3	0.61	2.9	44.8	4.39	197	–7.70	–5.38
	Avg. (S.D.)	**1.56 (0.90)**	**2.4**	**46.1 (2.2)**	**4.46 (0.08)**	**206 (13)**	**–7.77 (0.11)**	**–5.42 (0.05)**
	95% C.I.	2.24	1.0	5.3 (12%)	0.21 (5%)	33	0.28	0.12

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

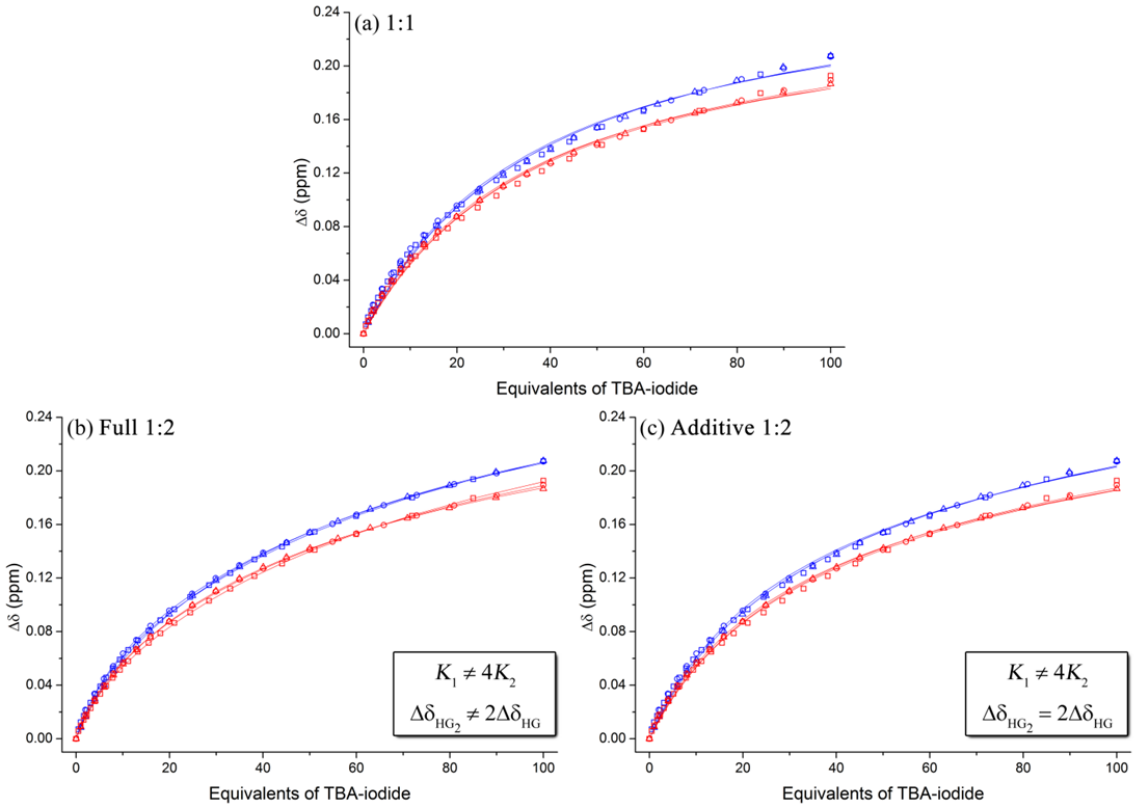


Figure S9. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-iodide in DMSO-d_6/acetone-d_6 (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** and **additive 1:2** are a quite different in cov_{fit} but both much better than **1:1**. Even after taking into account the smaller (n-df) for the **additive 1:2** model, the **full 1:2** appears significantly better, hence only the **full 1:2** need to be considered.

Table S7. Association constants of host 1 towards the nitrate anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-NO_3 in DMSO-d_6/acetone-d_6 (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	1.05	1	21.8	-	-	–7.64	-
	2	0.54	1	29.7	-	-	–8.41	-
	3	1.22	1	22.8	-	-	–7.74	-
	Avg. (S.D.)	**0.94 (0.36)**	**1**	**24.8 (4.3)**	-	-	**–7.93 (0.42)**	-
	95% C.I.	0.88	0	10.8 (43%)	-	-	1.04	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.06	18	70.1	5.46	383	–8.81	–5.92
	2	0.07	7.7	91.4	11.8	1080	–9.47	–7.84
	3	0.03	41	147	11.7	1720	–10.7	–7.80
	Avg. (S.D.)	**0.06 (0.02)**	**22**	**103 (40)**	**9.64 (3.62)**	**1060 (670)**	**–9.64 (0.93)**	**–7.19 (1.09)**
	95% C.I.	0.05	31	99 (96%)	9.00 (93%)	1660	2.32	2.72
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.49	2.1	35.7	3.93	140	–7.14	–5.11
	2	0.17	3.2	49.8	5.40	269	–7.97	–5.89
	3	0.44	2.8	38.3	4.05	155	–7.32	–5.18
	Avg. (S.D.)	**0.37 (0.17)**	**2.7**	**41.3 (7.5)**	**4.46 (0.81)**	**188 (70)**	**–7.47 (0.44)**	**–5.40 (0.43)**
	95% C.I.	0.43	1.0	18.7 (45%)	2.02 (45%)	175	1.08	1.08

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

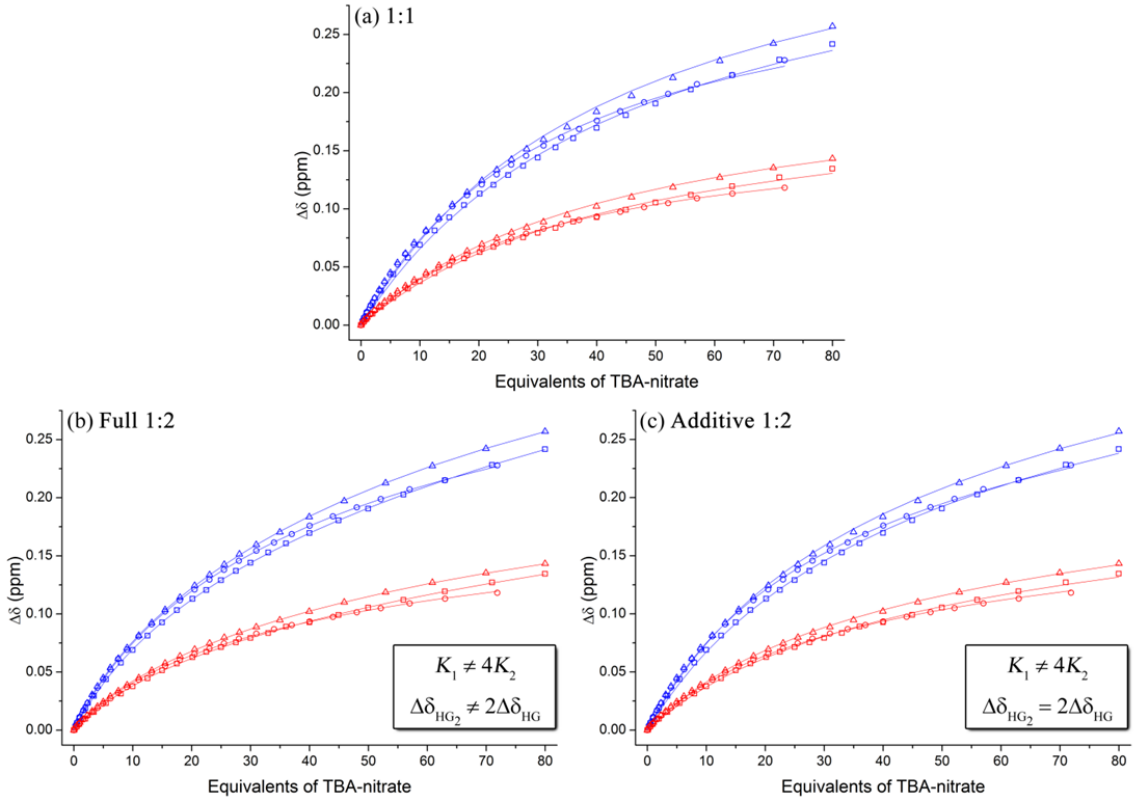


Figure S10. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-nitrate in DMSO-d_6/acetone-d_6 (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** and **additive 1:2** are quite different in cov_{fit} for all the experiments conducted but both much better than **1:1**. Even after taking into account the smaller (n-df) for the **additive 1:2** model, the **full 1:2** appears significantly better, hence only the **full 1:2** need to be considered

Table S8. Association constants of host 1 towards the acetate anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-acetate in $CDCl_3/CD_3CN$ (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	0.47	1	474	-	-	–15.3	-
	2	0.55	1	468	-	-	–15.2	-
	3	0.61	1	472	-	-	–15.3	-
	Avg. (S.D.)	**0.54 (0.07)**	**1**	**472 (3)**	-	-	**–15.3 (0.0)**	-
	95% C.I.	0.18	0	8 (2%)	-	-	0.0	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.06	7.8	531	–11.0[b]	-[b]	–13.8	-[b]
	2	0.06	9.2	525	–14.2[b]	-[b]	–13.8	-[b]
	3	0.03	20	573	–1.22[b]	-[b]	–14.0	-[b]
	Avg. (S.D.)	**0.05 (0.02)**	**12**	**543 (26)**	**–8.81 (6.77)**[b]	-[b]	**–13.9 (0.1)**	-[b]
	95% C.I.	0.04	13	66 (12%)	16.81 (191%)[b]	-[b]	0.3	-[b]
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.07	6.7	572	4.10	2340	–14.0	–5.21
	2	0.08	6.9	578	4.44	2570	–14.0	–5.41
	3	0.04	15	591	4.31	2540	–14.1	–5.34
	Avg. (S.D.)	**0.06 (0.02)**	**9.6**	**580 (9)**	**4.28 (0.17)**	**2490 (120)**	**–14.1 (0.0)**	**–5.32 (0.10)**
	95% C.I.	0.06	9.0	23 (4%)	0.43 (10%)	310	0.1	0.25

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b]Negative association constant obtained, hence calculation for β_{12} and ΔG are excluded.

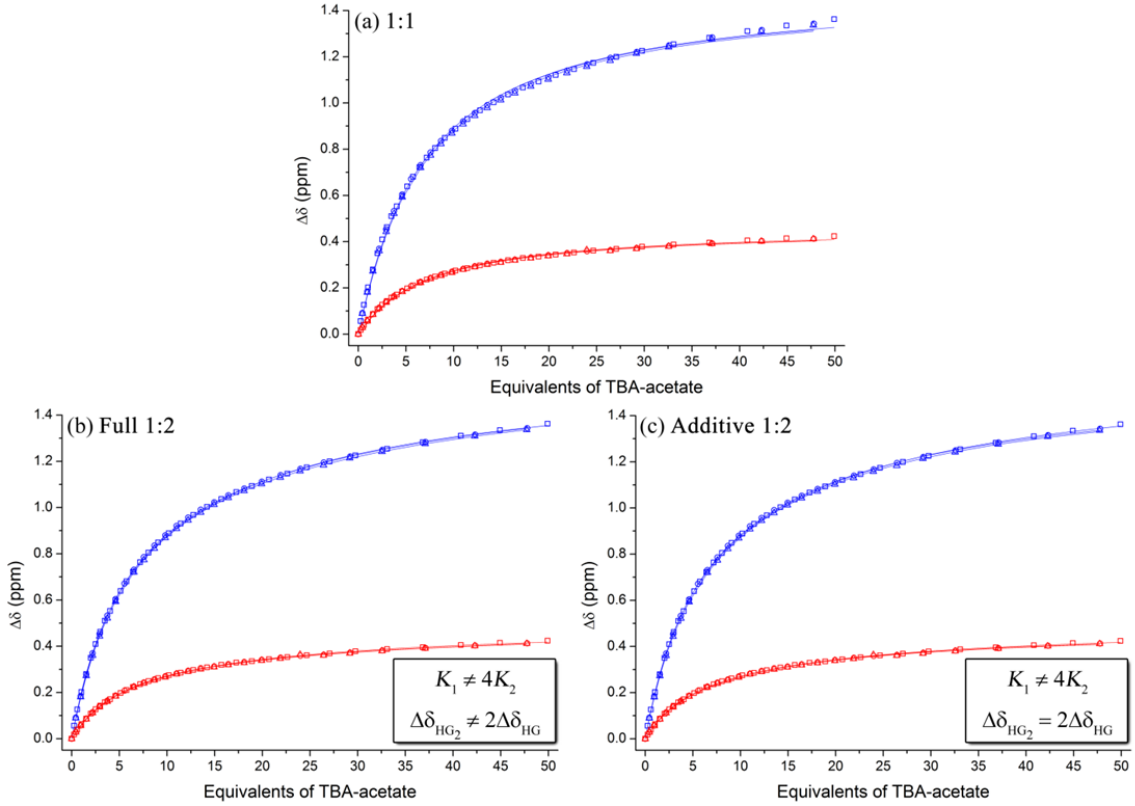


Figure S11. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-acetate in $CDCl_3/CD_3CN$ (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** shows a negative K_2 for all the experiments. The **additive 1:2** gives a much better cov_{fit} than the **1:1**. Hence only the **additive 1:2** binding model need to be considered.

Table S9. Association constants of host 1 towards the chloride anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-Cl in $CDCl_3/CD_3CN$ (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	0.37	1	177	-	-	–12.8	-
	2	0.70	1	196	-	-	–13.1	-
	3	0.64	1	193	-	-	–13.0	-
	Avg. (S.D.)	**0.57**	**1**	**189 (10)**	-	-	**–13.0 (0.1)**	-
	95% C.I.	0.18	0	25 (13%)	-	-	0.1	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.046	8.0	203	–1.51[b]	-[b]	–11.4	-[b]
	2	0.009	78	288	18.4	5300	–12.3	–8.94
	3	0.003	210	250	6.26	1560	–12.0	–6.26
	Avg. (S.D.)	**0.020 (0.024)**	**100**	**247 (43)**	**7.26 (10.04)**[b]	-[b]	**–11.9 (0.4)**	-[b]
	95% C.I.	0.058	192	106 (43%)	24.94 (323%)[b]	-[b]	1.1	-[b]
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.051	7.3	210	2.59	543	–11.5	–4.07
	2	0.027	26	248	3.69	914	–11.9	–4.95
	3	0.007	91	242	3.02	729	–11.9	–4.45
	Avg. (S.D.)	**0.028 (0.022)**	**42**	**233 (20)**	**3.10 (0.56)**	**729 (185)**	**–11.8 (0.2)**	**–4.49 (0.44)**
	95% C.I.	0.055	81	50 (22%)	1.38 (45%)	461	0.5	1.10

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b]Negative association constant obtained, hence calculation for β_{12} and ΔG are excluded.

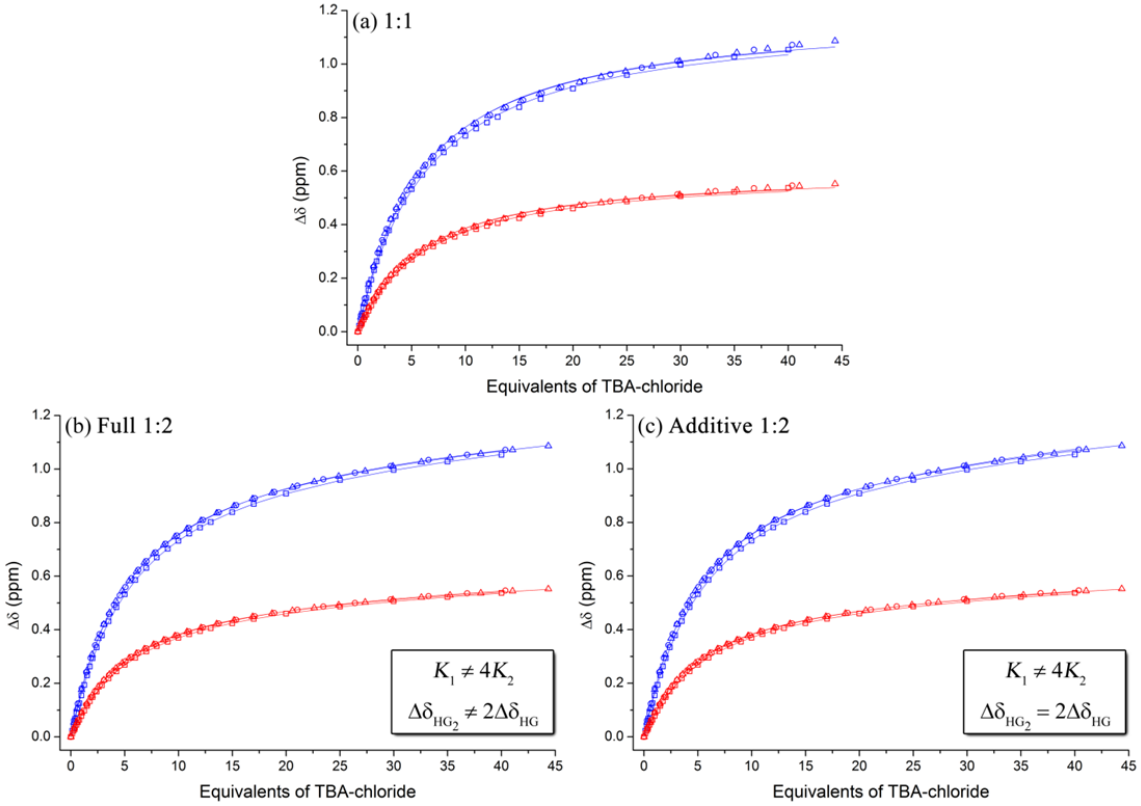


Figure S12. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-chloride in $CDCl_3/CD_3CN$ (1:9, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** shows a negative K_2 for one of the experiments. The **additive 1:2** gives a much better cov_{fit} than the **1:1**. Hence only the **additive 1:2** binding model need to be considered.

Table S10. Association constants of host 1 towards the acetate anion obtained from ^{1}H NMR titration (400 MHz, 298 K) of 1 (1.0 mM) with TBA-acetate in $CDCl_3/CD_3CN$ (1:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	0.67	1	156	-	-	–12.5	-
	2	0.41	1	158	-	-	–12.5	-
	3	0.42	1	153	-	-	–12.5	-
	Avg. (S.D.)	**0.50 (0.15)**	**1**	**156 (3)**	-	-	**–12.5 (0.0)**	-
	95% C.I.	0.36	0	6 (4%)	-	-	0.1	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.02	34	257	21.2	5460	–12.0	–9.28
	2	0.01	41	244	20.8	5070	–11.9	–9.23
	3	0.02	21	237	20.2	4780	–11.8	–9.17
	Avg. (S.D.)	**0.02 (0.01)**	**32**	**246 (11)**	**20.7 (0.5)**	**5100 (340)**	**–11.9 (0.1)**	**–9.23 (0.06)**
	95% C.I.	0.02	19	26 (11%)	1.2 (6%)	840	0.3	0.15
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.04	17	396	47.8	18900	–13.1	–11.3
	2	0.02	21	403	54.3	21900	–13.1	–11.6
	3	0.03	14	387	52.5	20300	–13.0	–11.5
	Avg. (S.D.)	**0.03 (0.01)**	**17**	**395 (8)**	**51.5 (3.4)**	**20400 (1500)**	**–13.1 (0.0)**	**–11.5 (0.2)**
	95% C.I.	0.02	6	17 (5%)	8.3 (16%)	3700	0.1	0.4

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

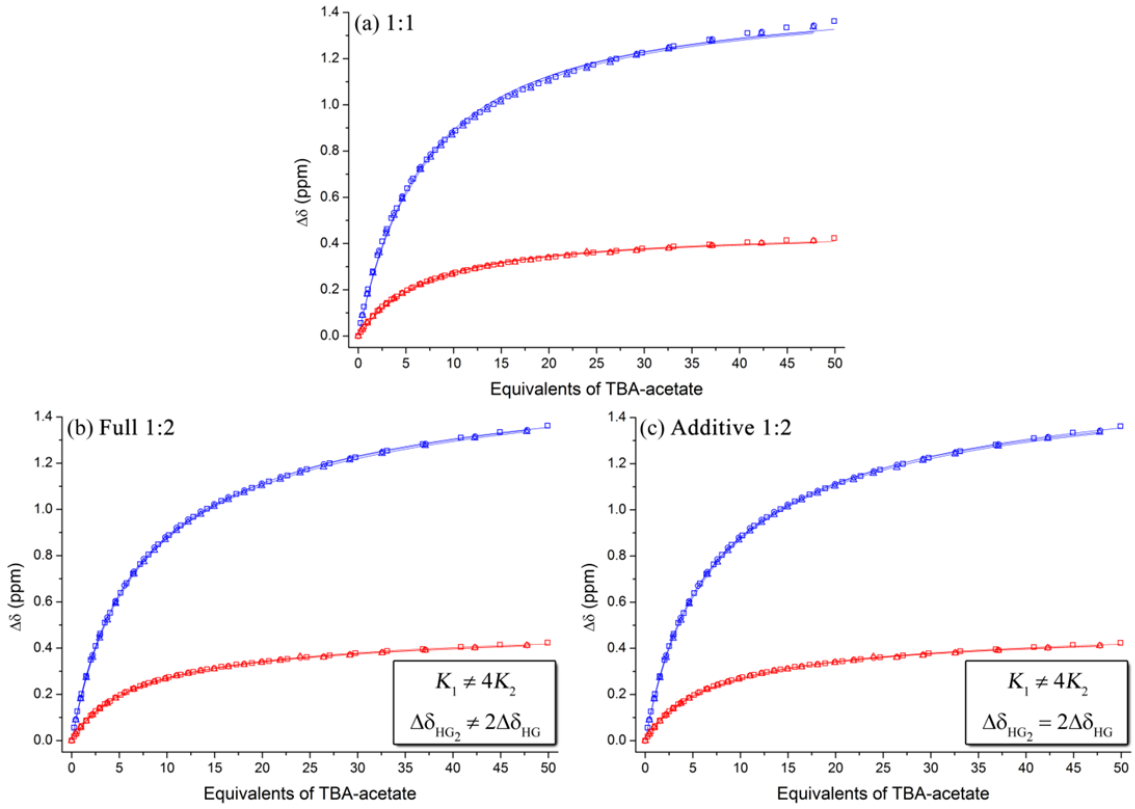


Figure S13. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-acetate in $CDCl_3/CD_3CN$ (1:1, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** and **additive 1:2** are a bit different in cov_{fit} but both much better than **1:1**. Given though the smaller (n-df) for the **additive 1:2** model, it is difficult to rule it inferior to the **full 1:2** despite of the difference in cov_{fit} between those two, hence both the **full 1:2** and **additive 1:2** binding model need to be considered.

Table S11. Association constants of host 1 towards chloride anion obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with TBA-Cl in $CDCl_3/CD_3CN$ (1:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 3)	1	0.63	1	64.3	-	-	–10.3	-
	2	0.74	1	64.4	-	-	–10.3	-
	3	0.62	1	65.9	-	-	–10.4	-
	Avg. (S.D.)	**0.66 (0.07)**	**1**	**64.9 (0.9)**	-	-	**–10.3 (0.0)**	-
	95% C.I.	0.16	0	2.2 (3%)	-	-	0.1	-
Full 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.008	79	184	24.7	4540	–11.2	–9.67
	2	0.01	74	162	21.5	3480	–10.9	–9.32
	3	0.016	39	167	23.4	3920	–11.0	–9.53
	Avg. (S.D.)	**0.01 (0.00)**	**64**	**171 (11)**	**23.2 (1.6)**	**3980 (530)**	**–11.0 (0.2)**	**–9.50 (0.18)**
	95% C.I.	0.01	40	28 (16%)	4.1 (17%)	1330	0.4	0.44
Additive 1:2 (n-df = 4) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.013	49	136	17.2	2350	–10.6	–8.77
	2	0.012	62	140	17.7	2480	–10.5	–8.84
	3	0.017	37	145	19.7	2860	–10.6	–9.10
	Avg. (S.D.)	**0.01 (0.00)**	**49**	**140 (4)**	**18.2 (1.3)**	**2560 (260)**	**–10.5 (0.1)**	**–8.90 (0.17)**
	95% C.I.	0.01	23	11 (8%)	3.2 (18%)	650	0.2	0.43

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

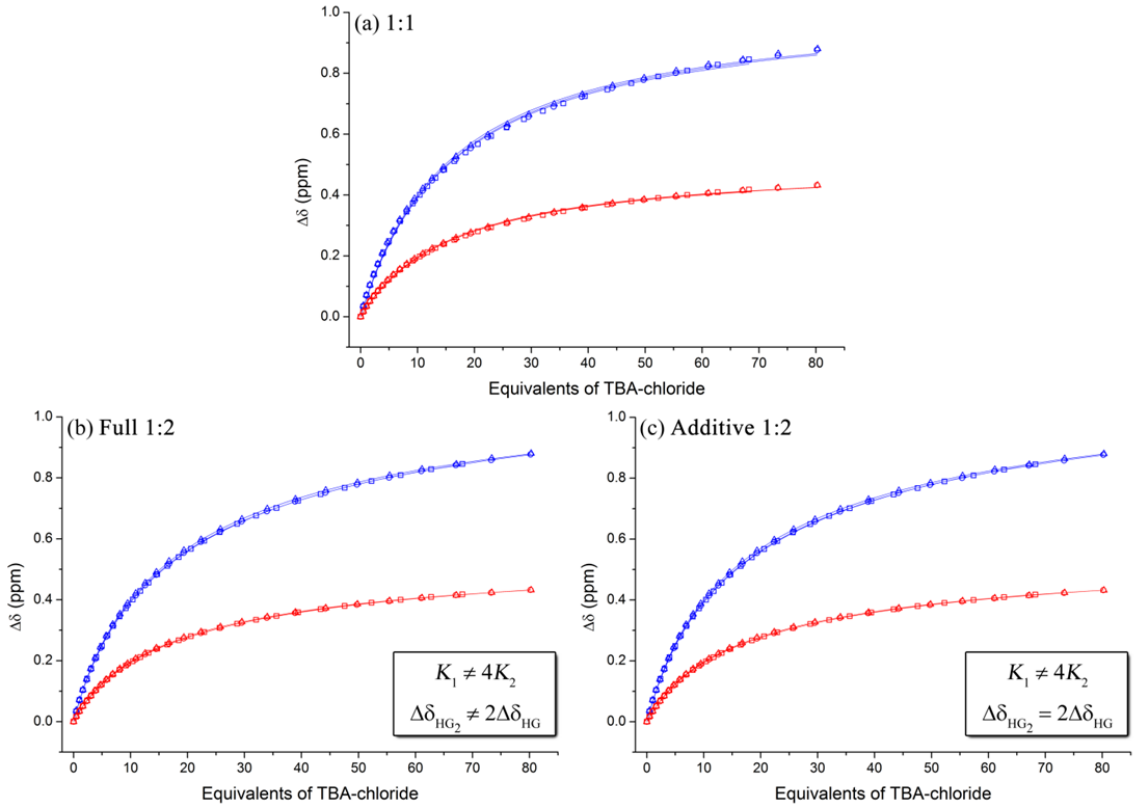


Figure S14. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with TBA-chloride in $CDCl_3/CD_3CN$ (1:1, v/v), showing the change in chemical shifts (Δδ) for amide-H (□, ○, △) and aromatic-H1 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to three different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**.

Conclusion: The **full 1:2** and **additive 1:2** are not too different in cov_{fit} but both much better than **1:1**. Given though the smaller (n-df) for the **additive 1:2** model, it is difficult to rule it inferior to the **full 1:2** despite of the difference in cov_{fit} between those two, hence both the **full 1:2** and **additive 1:2** binding model need to be considered.

6. Data Analysis for Cation Binding Studies

In all cases of cation binding studies for host **1**, four different proton resonances (ethylene-Hd, ethylene-He, aromatic-H3 and aromatic-H4) were recorded at every titration point, providing four sets of data for the binding models fitting analysis. Herein, the results from fitting to the **1:1** and all the four different 1:2 binding models, i.e., **full 1:2**, **additive 1:2**, **non-cooperative 1:2** and **statistical 1:2**, are reported for three different solvent mixtures; $CDCl_3/CD_3CN$ (1:9, v/v), $CDCl_3/CD_3CN$ (1:1, v/v) and $CDCl_3/CD_3OD$ (9:1, v/v). In the first solvent mixture, DMSO-d_6/acetone-d_6 (1:9, v/v), the titration of cation salts did not induce significant $\Delta\delta$ (< 0.05 ppm), thus no binding model fitting analysis was performed. In addition, the data from the titration of $NaClO_4$ in $CDCl_3/CD_3OD$ (9:1, v/v) was also fitted to the 2:1 binding model as discussed further in the main article.

Table S12. Association constants of host 1 towards the calcium dication obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $Ca(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	18.2	1	1.33×10^4	-	-	–23.5	-
	2	22.6	1	1.05×10^4	-	-	–22.9	-
	3	17.6	1	1.18×10^4	-	-	–23.2	-
	4	11.4	1	2.31×10^4	-	-	–24.9	-
	Average	**17.5**	**1**	$\mathbf{1.47 \times 10^4}$	-	-	**–23.6**	-
	Std. Dev.	4.6	0	0.57×10^4	-	-	0.9	-
	95% C.I.	7.4	0	0.91×10^4 (62%)	-	-	1.4	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.90	20	0.987×10^8	7.05×10^6	6.96×10^{14}	–43.9	–40.8
	2	0.65	35	2.83×10^8	2.52×10^6	7.14×10^{14}	–46.5	–38.3
	3	0.43	41	1.15×10^8	1.32×10^6	1.52×10^{14}	–44.3	–36.7
	4	1.15	10	0.0820×10^8	0.434×10^6	0.0356×10^{14}	–37.7	–33.9
	Average	**0.78**	**27**	$\mathbf{1.26 \times 10^8}$	$\mathbf{2.83 \times 10^6}$	$\mathbf{3.91 \times 10^{14}}$	**–43.1**	**–37.4**
	Std. Dev.	0.31	14	1.15×10^8	2.94×10^6	3.67×10^{14}	3.8	2.9
	95% C.I.	0.49	22	1.83×10^8 (145%)	4.68×10^6 (165%)	5.84×10^{14}	6.0	4.6
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	37.6	0.5	2.23×10^9	1.48×10^4	3.31×10^{13}	–51.6	–25.5
	2	22.4	1.0	6.42×10^3	–15.0[b]	-[b]	–20.0	-[b]
	3	17.5	1.0	7.28×10^3	–15.0[b]	-[b]	–20.3	-[b]
	4	11.3	1.0	1.55×10^4	–13.1[b]	-[b]	–22.2	-[b]
	Average	**22.2**	**0.9**	$\mathbf{5.59 \times 10^8}$	-[b]	-[b]	**–28.5**	-[b]
	Std. Dev.	11.2	0.3	11.17×10^8	-[b]	-[b]	15.4	-[b]
	95% C.I.	17.9	0.4	17.78×10^8 (318%)	-[b]	-[b]	24.5	-[b]
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.99	18	2.81×10^7	7.02×10^6	19.7×10^{13}	–40.8	–40.8
	2	1.30	17	1.04×10^7	2.60×10^6	2.71×10^{13}	–38.3	–38.3
	3	0.96	18	0.844×10^7	2.11×10^6	1.78×10^{13}	–37.8	–37.8
	4	1.34	8.5	0.228×10^7	0.570×10^6	0.130×10^{13}	–34.6	–34.6
	Average	**1.15**	**16**	$\mathbf{1.23 \times 10^7}$	$\mathbf{3.07 \times 10^6}$	$\mathbf{6.08 \times 10^{13}}$	**–37.9**	**–37.9**
	Std. Dev.	0.20	4.8	1.11×10^7	2.77×10^6	9.14×10^{13}	2.6	2.6
	95% C.I.	0.32	7.6	1.76×10^7 (143%)	4.40×10^6 (143%)	14.54×10^{13}	4.1	4.1
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	38.2	0.5	7.72×10^5	1.93×10^5	14.9×10^{10}	–31.9	–31.9
	2	47.2	0.5	1.71×10^5	0.427×10^5	0.729×10^{10}	–28.1	–28.1
	3	36.8	0.5	7.68×10^5	1.92×10^5	14.8×10^{10}	–31.9	–31.9
	4	43.8	0.3	1.31×10^5	0.328×10^5	0.430×10^{10}	–27.5	–27.5
	Average	**41.5**	**0.4**	$\mathbf{4.60 \times 10^5}$	$\mathbf{1.15 \times 10^5}$	$\mathbf{7.70 \times 10^{10}}$	**–29.8**	**–29.8**
	Std. Dev.	4.9	0.1	3.58×10^5	0.895×10^5	8.23×10^{10}	2.4	2.4
	95% C.I.	7.7	0.2	5.69×10^5 (124%)	1.42×10^5 (124%)	13.1×10^{10}	3.8	3.8

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b]Negative association constant obtained, hence calculation for β_{12} and ΔG are excluded.

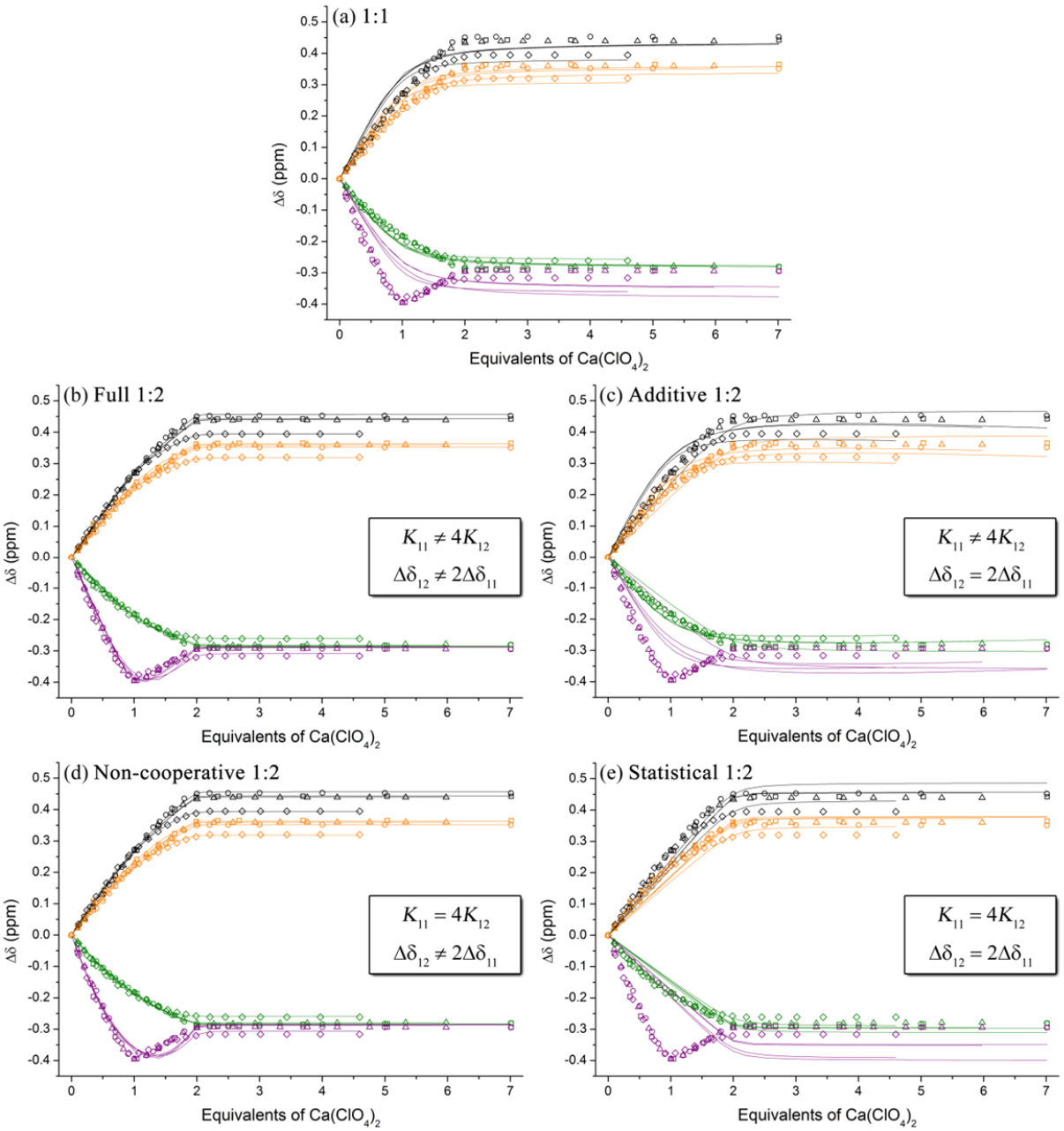


Figure S15. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $Ca(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:9, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △, ◇), ethylene-He (□, ○, △, ◇), aromatic-H3 (□, ○, △, ◇) and aromatic-H4 (□, ○, △, ◇); symbols indicate the order of the quadruplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 1:2** and **non-cooperative 1:2** model can describe this data much better than the other three models. The associations constants are though much greater than could reliably estimate from ^{1}H NMR titrations. The main article will therefore indicate that the binding is too strong to be measured by ^{1}H NMR titrations but that qualitatively both the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best.

Table S13. Association constants of host 1 towards the magnesium dication obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $Mg(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	4.57	1	3.26×10^3	-	-	–20.0	-
	2	3.51	1	3.41×10^3	-	-	–20.2	-
	3	4.59	1	3.11×10^3	-	-	–19.9	-
	Average	**4.22**	**1**	$\mathbf{3.26 \times 10^3}$	-	-	**–20.0**	-
	Std. Dev.	0.61	0	0.15×10^3	-	-	0.1	-
	95% C.I.	1.52	0	0.37×10^3 (11%)	-	-	0.3	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	1.04	4.4	8.06×10^4	231	1.86×10^7	–26.3	–15.2
	2	0.80	4.4	2.02×10^4	177	0.356×10^7	–22.8	–14.5
	3	0.55	8.3	6.74×10^4	112	0.753×10^7	–25.8	–13.4
	Average	**0.80**	**5.7**	$\mathbf{5.61 \times 10^4}$	**173**	$\mathbf{0.990 \times 10^7}$	**–25.0**	**–14.4**
	Std. Dev.	0.24	2.3	3.17×10^4	59	0.781×10^7	1.9	0.9
	95% C.I.	0.60	5.7	7.88×10^4 (141%)	148 (86%)	1.94×10^7	4.6	2.3
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	3.20	1.4	2.91×10^4	83.8	2.44×10^6	–23.8	–12.7
	2	2.80	1.3	0.899×10^4	34.7	0.312×10^6	–20.8	–10.5
	3	2.30	2.0	9.52×10^4	118	11.3×10^6	–26.7	–13.5
	Average	**2.77**	**1.6**	$\mathbf{4.44 \times 10^4}$	**78.9**	$\mathbf{4.67 \times 10^6}$	**–23.8**	**–12.3**
	Std. Dev.	0.45	0.4	4.51×10^4	42.0	5.81×10^6	2.9	1.6
	95% C.I.	1.12	1.0	11.21×10^4 (252%)	104.4 (132%)	14.43×10^6	7.3	3.9
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	4.30	1.1	3.58×10^3	895	3.20×10^6	–18.6	–18.6
	2	3.20	1.1	3.59×10^3	898	3.22×10^6	–18.6	–18.6
	3	4.80	1.0	3.30×10^3	825	2.73×10^6	–18.4	–18.4
	Average	**4.10**	**1.0**	$\mathbf{3.49 \times 10^3}$	**873**	$\mathbf{3.05 \times 10^6}$	**–18.5**	**–18.5**
	Std. Dev.	0.82	0.1	0.16×10^3	41	0.28×10^6	0.1	0.1
	95% C.I.	2.03	0.2	0.41×10^3 (12%)	102 (12%)	0.70×10^6	0.3	0.3
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	19.4	0.2	2.16×10^4	5.39×10^3	1.16×10^8	–23.0	–23.0
	2	17.9	0.2	2.97×10^4	7.42×10^3	2.21×10^8	–23.8	–23.8
	3	16.0	0.3	1.88×10^4	4.69×10^3	0.879×10^8	–22.7	–22.7
	Average	**17.8**	**0.2**	$\mathbf{2.33 \times 10^4}$	$\mathbf{5.84 \times 10^3}$	$\mathbf{1.42 \times 10^8}$	**–23.2**	**–23.2**
	Std. Dev.	1.7	0.05	0.57×10^4	1.42×10^3	0.70×10^8	0.6	0.6
	95% C.I.	4.2	0.1	1.41×10^4 (60%)	3.53×10^3 (60%)	1.73×10^8	1.4	1.4

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

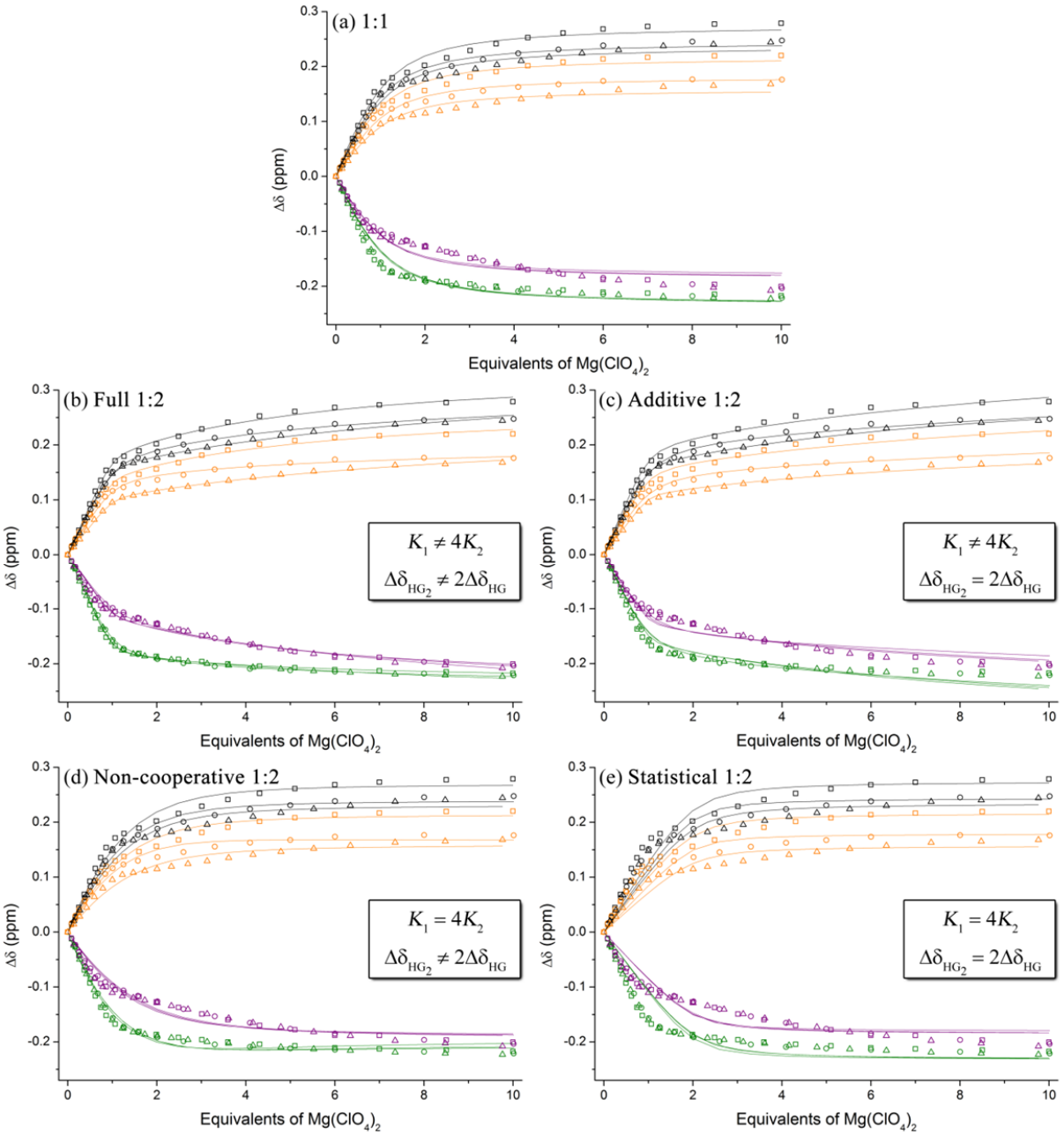


Figure S16. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $Mg(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:9, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: The cov_{fit} for the **full 1:2** model is significantly better than all the other binding models and visual inspection of the binding isotherms appears to confirm this. We conclude therefore that the **full 1:2** binding model describes this data best.

Table S14. Association constants of host 1 towards the sodium cation obtained from ^{1}H NMR titration (400 MHz, 298 K) of 1 (1.0 mM) with $NaClO_4$ in $CDCl_3/CD_3CN$ (1:9, v/v); and comparison of the binding models.

Binding Model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	1.27	1	117	-	-	–11.8	-
	2	0.22	1	104	-	-	–11.5	-
	3	0.22	1	105	-	-	–11.5	-
	Average	**0.57**	**1**	**108**	-	-	**–11.6**	-
	Std. Dev.	0.60	0	7	-	-	0.2	-
	95% C.I.	1.50	0	18 (17%)	-	-	0.4	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.12	11	16400	74.2	12.2×10^5	–22.3	–12.4
	2	0.08	2.8	479	64.1	0.307×10^5	–13.6	–12.0
	3	0.07	3.1	1280	77.8	0.994×10^5	–16.0	–12.5
	Average	**0.09**	**5.5**	**6060**	**72.0**	$\mathbf{4.50 \times 10^5}$	**–17.3**	**–12.3**
	Std. Dev.	0.03	4.4	8980	7.1	6.67×10^5	4.5	0.3
	95% C.I.	0.07	11	22300 (368%)	17.7 (25%)	16.58×10^5	11.2	0.6
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.64	2.0	335	33.9	1.14×10^4	–12.7	–10.5
	2	0.19	1.2	244	45.7	1.12×10^4	–11.9	–11.2
	3	0.20	1.1	247	46.6	1.15×10^4	–11.9	–11.2
	Average	**0.34**	**1.4**	**276**	**42.1**	$\mathbf{1.14 \times 10^4}$	**–12.2**	**–11.0**
	Std. Dev.	0.26	0.5	52	7.1	0.02×10^4	0.4	0.4
	95% C.I.	0.64	1.2	128 (47%)	17.6 (42%)	0.05×10^4	1.1	1.1
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	1.30	1.0	214	53.5	11.5×10^3	–11.6	–11.6
	2	0.14	1.6	191	47.8	9.15×10^3	–11.3	–11.3
	3	0.14	1.6	194	48.4	9.37×10^3	–11.3	–11.3
	Average	**0.52**	**1.4**	**200**	**49.9**	$\mathbf{9.99 \times 10^3}$	**–11.4**	**–11.4**
	Std. Dev.	0.67	0.3	13	3.2	1.28×10^3	0.2	0.2
	95% C.I.	1.67	0.9	31 (16%)	7.8 (16%)	3.18×10^3	0.4	0.4
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	1.50	0.8	253	63.0	1.60×10^4	–12.0	–12.0
	2	0.25	0.9	222	55.4	1.23×10^4	–11.7	–11.7
	3	0.26	0.8	224	56.1	1.26×10^4	–11.7	–11.7
	Average	**0.67**	**0.9**	**233**	**58.2**	$\mathbf{1.36 \times 10^4}$	**–11.8**	**–11.8**
	Std. Dev.	0.72	0.02	17	4.4	0.21×10^4	0.2	0.2
	95% C.I.	1.78	0.05	43 (19%)	10.8 (19%)	0.52×10^4	0.5	0.5

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

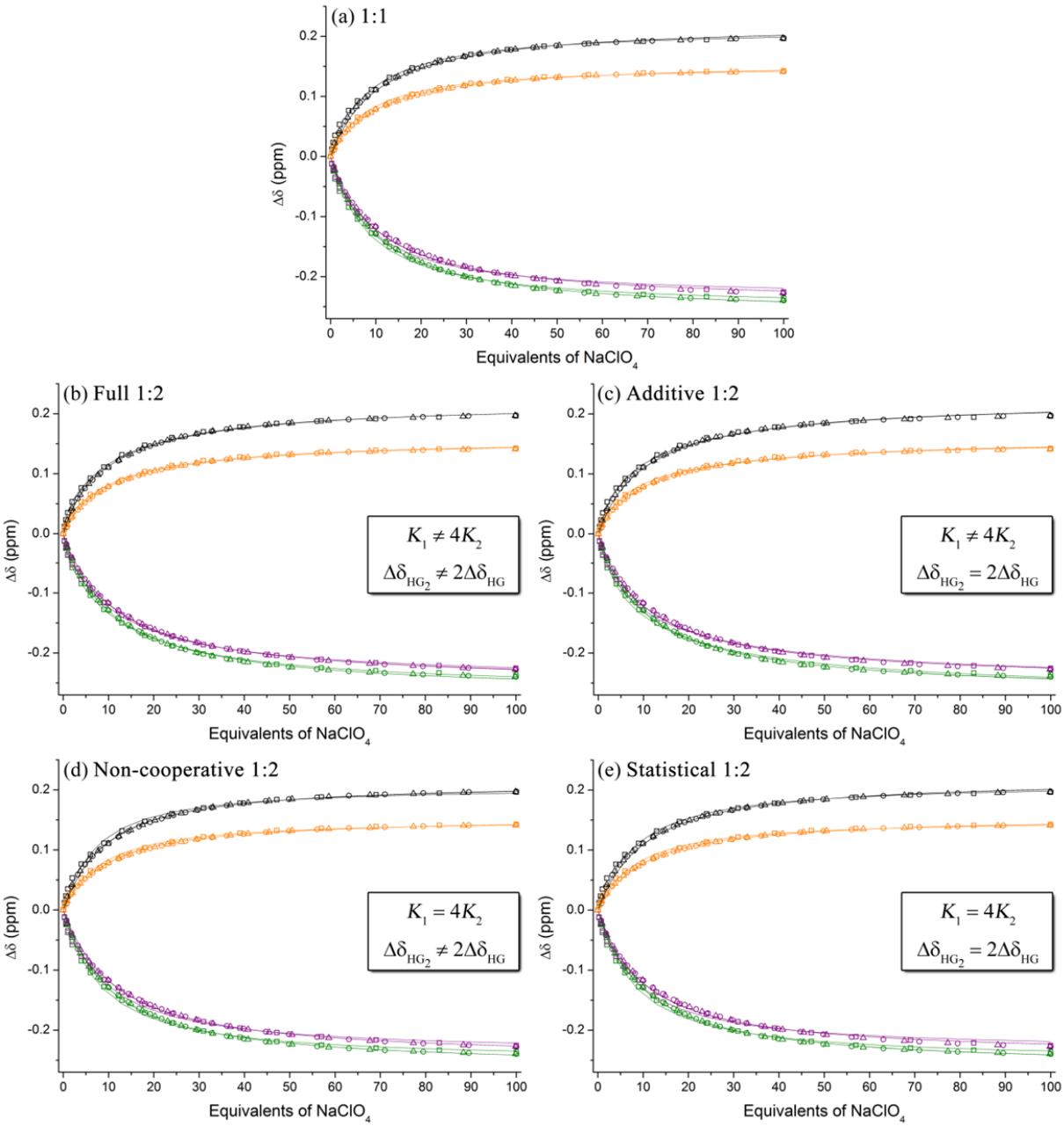


Figure S17. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $NaClO_4$ in $CDCl_3/CD_3CN$ (1:9, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: The cov_{fit} for the **full 1:2** model is better than all the other binding models with additive 1:2 and non-cooperative 1:2 equal second. However the standard deviation for the full 1:2 model is very high. We conclude therefore that the **full 1:2**, **additive 1:2 and non-cooperative 1:2** binding models all need to be consideredt.

Table S15. Association constants of host 1 towards the potassium cation obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with KPF_6 in $CDCl_3/CD_3CN$ (1:9, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	1.53	1	39.8	-	-	–9.13	-
	2	0.46	1	37.3	-	-	–8.97	-
	3	0.44	1	38.9	-	-	–9.07	-
	Average	**0.81**	**1**	**38.7**	-	-	**–9.06**	-
	Std. Dev.	0.63	0	1.3	-	-	0.08	-
	95% C.I.	1.56	0	3.2 (8%)	-	-	0.20	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.52	2.9	70.4	0.710	50.0	–8.82	–0.868
	2	0.01	46	69.2	4.82	334	–8.78	–5.62
	3	0.01	44	67.0	3.27	220	–8.70	–4.66
	Average	**0.18**	**31**	**68.9**	**2.94**	**201**	**–8.77**	**–3.71**
	Std. Dev.	0.29	24	1.7	2.08	143	0.06	2.51
	95% C.I.	0.72	60	4.2 (6%)	5.16 (176%)	355	0.15	6.24
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.96	1.6	70.6	5.00	353	–8.83	–5.71
	2	0.23	2.0	66.3	6.01	398	–8.67	–6.16
	3	0.23	1.9	68.1	6.37	434	–8.74	–6.30
	Average	**0.47**	**1.8**	**68.3**	**5.79**	**395**	**–8.75**	**–6.06**
	Std. Dev.	0.43	0.2	2.2	0.71	40	0.08	0.31
	95% C.I.	1.05	0.5	5.4 (8%)	1.76 (30%)	100	0.19	0.78
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	1.20	1.3	76.7	19.2	1470	–9.04	–9.04
	2	0.28	1.6	71.4	17.9	1280	–8.86	–8.86
	3	0.27	1.6	74.5	18.6	1390	–8.96	–8.96
	Average	**0.58**	**1.5**	**74.2**	**18.6**	**1380**	**–8.95**	**–8.95**
	Std. Dev.	0.53	0.2	2.6	0.7	100	0.09	0.09
	95% C.I.	1.33	0.5	6.6 (9%)	1.6 (9%)	240	0.22	0.22
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	1.60	1.0	82.7	20.7	1710	–9.22	–9.22
	2	0.48	1.0	77.2	19.3	1490	–9.05	–9.05
	3	0.46	1.0	80.7	20.2	1630	–9.16	–9.16
	Average	**0.85**	**1.0**	**80.2**	**20.0**	**1610**	**–9.15**	**–9.15**
	Std. Dev.	0.65	0.0	2.8	0.7	110	0.09	0.09
	95% C.I.	1.62	0.0	6.9 (9%)	1.7 (9%)	280	0.21	0.21

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

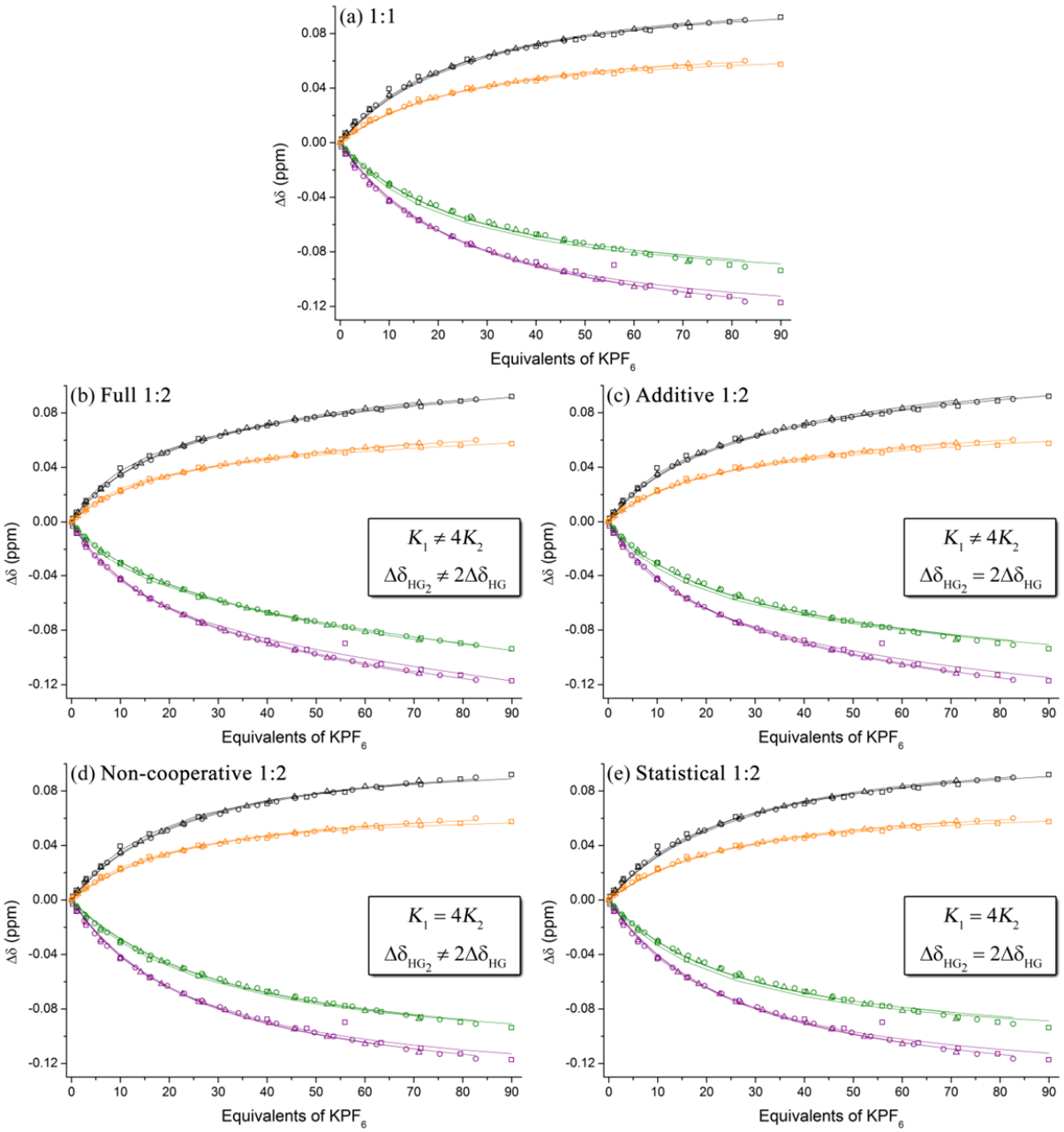


Figure S18. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with KPF_6 in $CDCl_3/CD_3CN$ (1:9, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: The cov_{fit} for the **full 1:2** model is better than all the other binding models. We conclude therefore that the **full 1:2** binding model describes this data best.

Table S16. Association constants of host 1 towards the calcium dication obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $Ca(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	24.8	1	9.49×10^3	-	-	–22.7	-
	2	23.7	1	9.34×10^3	-	-	–22.7	-
	3	22.6	1	10.1×10^3	-	-	–22.8	-
	Average	**23.7**	**1**	$\mathbf{9.64 \times 10^3}$	-	-	**–22.7**	-
	Std. Dev.	1.1	0	0.40×10^3	-	-	0.1	-
	95% C.I.	2.8	0	1.00×10^3 (10%)	-	-	0.3	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.77	32	3.57×10^8	5.08×10^6	1.81×10^{15}	–47.1	–40.0
	2	0.78	30	5.24×10^8	6.84×10^6	3.59×10^{15}	–48.0	–40.7
	3	0.91	25	4.31×10^8	5.55×10^6	2.39×10^{15}	–47.5	–40.2
	Average	**0.82**	**29**	$\mathbf{4.38 \times 10^8}$	$\mathbf{5.82 \times 10^6}$	$\mathbf{2.60 \times 10^{15}}$	**–47.6**	**–40.3**
	Std. Dev.	0.08	4	0.84×10^8	0.91×10^6	0.90×10^{15}	0.5	0.4
	95% C.I.	0.20	10	2.08×10^8 (47%)	2.27×10^6 (39%)	2.24×10^{15}	1.2	0.9
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	24.7	1.0	4.09×10^3	–37.8[b]	-[b]	–18.9	-[b]
	2	23.5	1.0	3.83×10^3	–40.0[b]	-[b]	–18.7	-[b]
	3	22.4	1.0	4.52×10^3	–35.6[b]	-[b]	–19.1	-[b]
	Average	**23.5**	**1.0**	$\mathbf{4.15 \times 10^3}$	**–37.8**[b]	-[b]	**–18.9**	-[b]
	Std. Dev.	1.2	0.0	0.35×10^3	2.2[b]	-[b]	0.2	-[b]
	95% C.I.	2.9	0.0	0.86×10^3 (21%)	5.5 (15%)[b]	-[b]	0.5	-[b]
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	1.54	16	2.05×10^7	5.13×10^6	1.05×10^{14}	–40.0	–40.0
	2	1.55	15	2.62×10^7	6.55×10^6	1.71×10^{14}	–40.6	–40.6
	3	1.66	14	2.23×10^7	5.58×10^6	1.25×10^{14}	–40.2	–40.2
	Average	**1.58**	**15**	$\mathbf{2.30 \times 10^7}$	$\mathbf{5.75 \times 10^6}$	$\mathbf{1.34 \times 10^{14}}$	**–40.3**	**–40.3**
	Std. Dev.	0.07	1	0.29×10^7	0.73×10^6	0.34×10^{14}	0.3	0.3
	95% C.I.	0.17	3	0.72×10^7 (31%)	1.80×10^6 (31%)	0.85×10^{14}	0.8	0.8
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	47.9	0.5	1.11×10^5	2.77×10^4	3.06×10^9	–27.1	–27.1
	2	45.3	0.5	1.32×10^5	3.30×10^4	4.36×10^9	–27.5	–27.5
	3	45.0	0.5	1.16×10^5	2.89×10^4	3.35×10^9	–27.2	–27.2
	Average	**46.1**	**0.5**	$\mathbf{1.19 \times 10^5}$	$\mathbf{2.99 \times 10^4}$	$\mathbf{3.59 \times 10^9}$	**–27.2**	**–27.2**
	Std. Dev.	1.6	0.01	0.11×10^5	0.28×10^4	0.68×10^9	0.2	0.2
	95% C.I.	4.0	0.03	0.28×10^5 (23%)	0.69×10^4 (23%)	1.68×10^9	0.6	0.6

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b]Negative association constant obtained, hence calculation for β_{12} and ΔG are excluded.

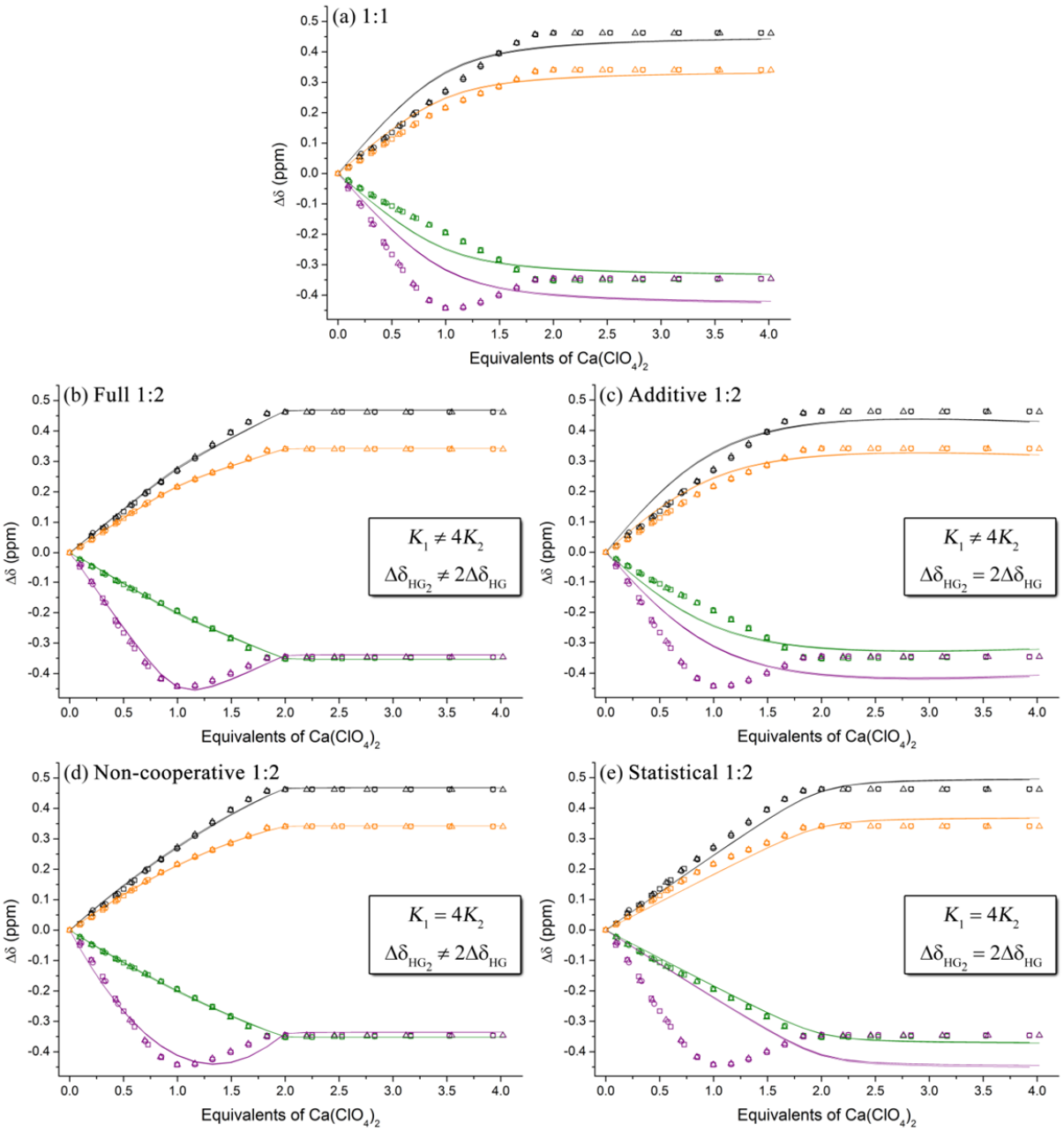


Figure S19. ^{1}H NMR titration (400MHz, 298 K) of host **1** (1.0 mM) with $Ca(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:1, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 1:2** and **non-cooperative 1:2** model can describe this data much better than the other three models. The associations constants are though much greater than could reliably estimate from ^{1}H NMR titrations. The main article will therefore indicate that the binding is too strong to be measured by ^{1}H NMR titrations but that qualitatively both the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best.

Table S17. Association constants of host 1 towards the magnesium dication obtained from ^{1}H NMR titration (400 MHz, 298 K) of 1 (1.0 mM) with $Mg(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	2.80	1	1.80×10^3	-	-	–18.6	-
	2	2.49	1	1.87×10^3	-	-	–18.7	-
	3	2.32	1	1.86×10^3	-	-	–18.6	-
	Average	**2.54**	**1**	$\mathbf{1.84 \times 10^3}$	-	-	**–18.6**	-
	Std. Dev.	0.25	0	0.04×10^3	-	-	0.1	-
	95% C.I.	0.61	0	0.09×10^3 (5%)	-	-	0.2	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.65	4.3	4.14×10^3	1060	4.38×10^6	–18.9	–19.0
	2	0.52	4.8	4.83×10^3	907	4.39×10^6	–19.3	–18.6
	3	0.47	4.9	3.84×10^3	667	2.56×10^6	–18.7	–17.8
	Average	**0.55**	**4.7**	$\mathbf{4.27 \times 10^3}$	**878**	$\mathbf{3.78 \times 10^6}$	**–19.0**	**–18.5**
	Std. Dev.	0.10	0.3	0.51×10^3	198	1.05×10^6	0.3	0.6
	95% C.I.	0.24	0.8	1.26×10^3 (30%)	491 (56%)	2.61×10^6	0.7	1.4
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	2.50	1.1	1.26×10^3	–11.5[b]	-[b]	–16.0	-[b]
	2	2.30	1.1	1.29×10^7	1630	2.10×10^{10}	–38.8	–20.0
	3	2.20	1.1	1.45×10^3	–8.90[b]	-[b]	–16.3	-[b]
	Average	**2.33**	**1.1**	$\mathbf{4.30 \times 10^6}$	**536**[b]	-[b]	**–23.7**	-[b]
	Std. Dev.	0.15	0.0	7.44×10^6	947[b]	-[b]	13.1	-[b]
	95% C.I.	0.38	0.1	1.85×10^7 (430%)	2350 (438%)[b]	-[b]	32.6	-[b]
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.66	4.2	4.25×10^3	1060	4.52×10^6	–19.0	–19.0
	2	0.52	4.8	3.46×10^3	875	3.00×10^6	–18.5	–18.5
	3	0.49	4.7	2.72×10^3	681	1.85×10^6	–17.9	–17.9
	Average	**0.55**	**4.6**	$\mathbf{3.48 \times 10^3}$	**870**	$\mathbf{3.12 \times 10^6}$	**–18.4**	**–18.4**
	Std. Dev.	0.09	0.3	0.77×10^3	191	1.34×10^6	0.6	0.6
	95% C.I.	0.22	0.7	1.90×10^3 (55%)	475 (55%)	3.32×10^6	1.4	1.4
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	3.70	0.8	1.60×10^4	4.00×10^3	6.39×10^7	–22.3	–22.3
	2	3.80	0.7	1.58×10^4	3.96×10^3	6.27×10^7	–22.2	–22.2
	3	4.10	0.6	1.61×10^4	4.01×10^3	6.45×10^7	–22.3	–22.3
	Average	**3.87**	**0.7**	$\mathbf{1.60 \times 10^4}$	$\mathbf{3.99 \times 10^3}$	$\mathbf{6.37 \times 10^7}$	**–22.3**	**–22.3**
	Std. Dev.	0.21	0.1	0.01×10^4	0.03×10^3	0.09×10^7	0.0	0.0
	95% C.I.	0.52	0.2	0.03×10^4 (2%)	0.07×10^3 (2%)	0.23×10^7	0.0	0.0

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b]Negative association constant obtained, hence calculation for β_{12} and ΔG are excluded.

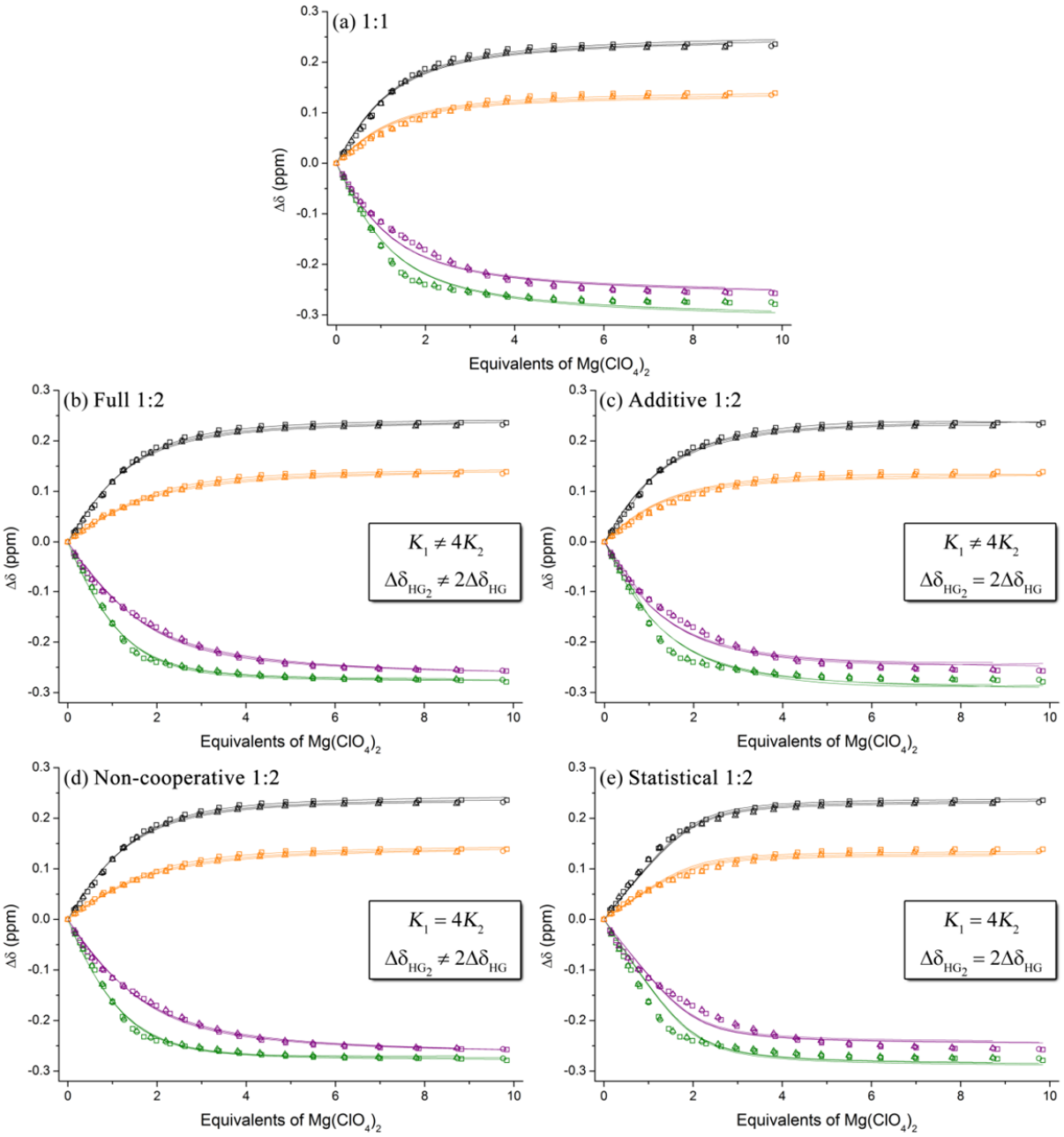


Figure S20. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $Mg(ClO_4)_2$ in $CDCl_3/CD_3CN$ (1:1, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 1:2** and **non-cooperative 1:2** model can describe this data much better than the other three models. We conclude therefore that the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best.

Table S18. Association constants of host 1 towards the sodium cation obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $NaClO_4$ in $CDCl_3/CD_3CN$ (1:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	0.29	1	219	-	-	–13.4	-
	2	0.27	1	332	-	-	–14.4	-
	3	0.26	1	338	-	-	–14.4	-
	Average	**0.27**	**1**	**296**	-	-	**–14.1**	-
	Std. Dev.	0.01	0	67	-	-	0.6	-
	95% C.I.	0.03	0	166 (56%)	-	-	1.5	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.17	1.7	228	13.8	3.16×10^3	–11.7	–8.23
	2	0.06	4.5	299	27.3	8.16×10^3	–12.4	–9.91
	3	0.04	6.5	309	30.2	9.32×10^3	–12.5	–10.2
	Average	**0.09**	**4.2**	**279**	**23.8**	$\mathbf{6.88 \times 10^3}$	**–12.2**	**–9.43**
	Std. Dev.	0.07	2.4	44	8.7	3.27×10^3	0.4	1.05
	95% C.I.	0.17	6.0	109 (39%)	21.6 (91%)	8.13×10^3	1.0	2.61
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.29	1.0	573	104	0.598×10^5	–14.0	–13.2
	2	0.17	1.6	772	208	1.60×10^5	–14.8	–14.9
	3	0.17	1.5	807	208	1.68×10^5	–14.9	–14.9
	Average	**0.21**	**1.4**	**717**	**174**	$\mathbf{1.29 \times 10^5}$	**–14.5**	**–14.4**
	Std. Dev.	0.06	0.3	126	60	0.60×10^5	0.5	1.0
	95% C.I.	0.16	0.8	314 (44%)	149 (86%)	1.50×10^5	1.1	2.4
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.23	1.3	364	90.9	3.30×10^4	–12.9	–12.9
	2	0.12	2.3	781	195	15.2×10^4	–14.8	–14.8
	3	0.05	5.2	362	90.5	3.28×10^4	–12.9	–12.9
	Average	**0.13**	**2.9**	**502**	**126**	$\mathbf{7.27 \times 10^4}$	**–13.5**	**–13.5**
	Std. Dev.	0.09	2.0	241	60	6.89×10^4	1.1	1.1
	95% C.I.	0.22	5.1	599 (119%)	150 (119%)	17.13×10^4	2.7	2.7
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.38	0.8	502	125	6.30×10^4	–13.7	–13.7
	2	0.15	1.8	297	74.2	2.20×10^4	–12.4	–12.4
	3	0.17	1.5	820	205	16.8×10^4	–14.9	–14.9
	Average	**0.24**	**1.4**	**540**	**135**	$\mathbf{8.44 \times 10^4}$	**–13.7**	**–13.7**
	Std. Dev.	0.13	0.5	264	66	7.54×10^4	1.3	1.3
	95% C.I.	0.31	1.3	655 (121%)	164 (121%)	18.74×10^4	3.1	3.1

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

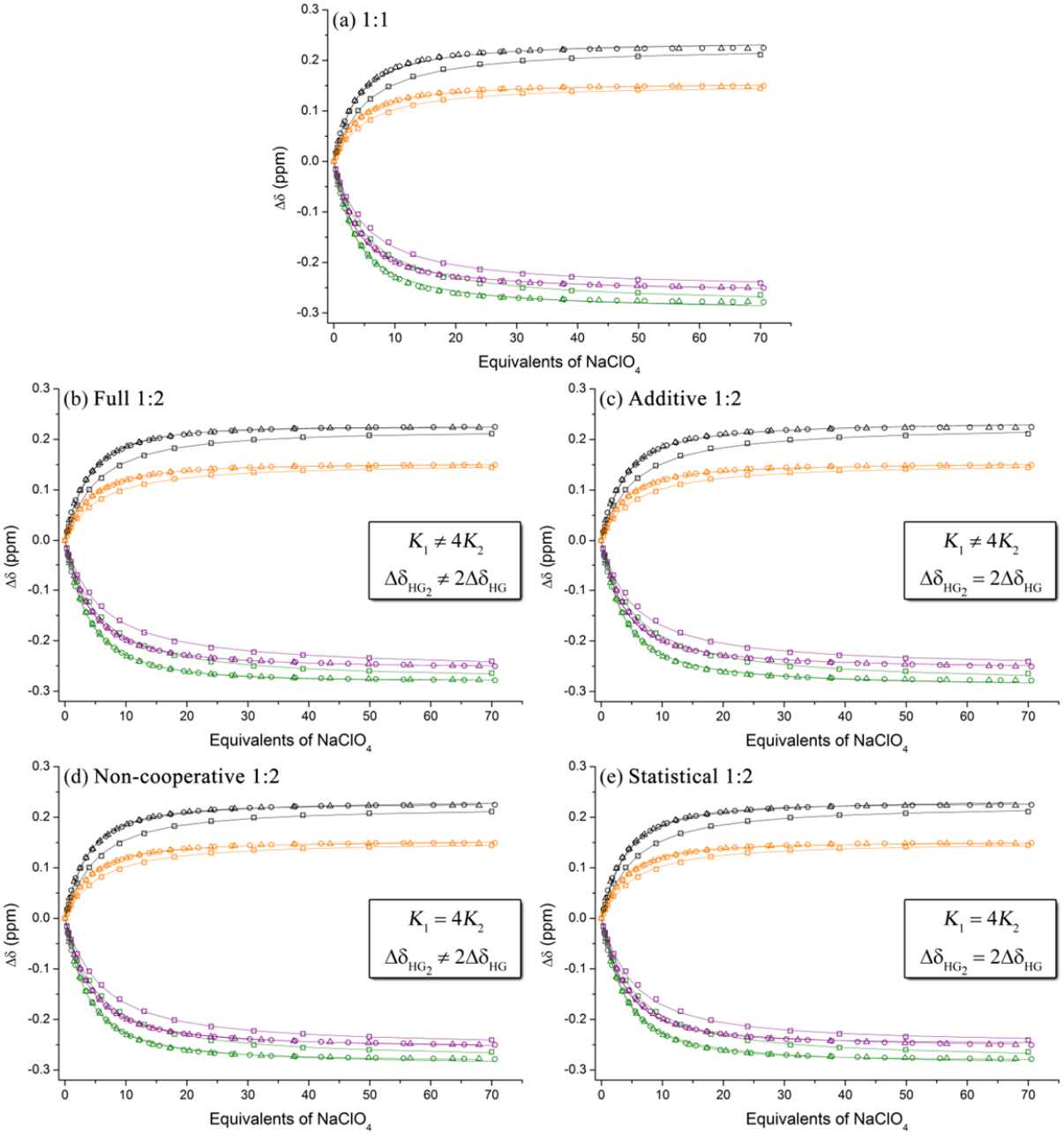


Figure S21. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $NaClO_4$ in $CDCl_3/CD_3CN$ (1:1, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 1:2** and **non-cooperative 1:2** model can describe this data better than the other three models. We conclude therefore that the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best.

Table S19. Association constants of host 1 towards the calcium dication obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $Ca(ClO_4)_2$ in $CDCl_3/CD_3OD$ (9:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	1.69	1	3.45×10^3	-	-	–20.2	-
	2	0.81	1	4.16×10^3	-	-	–20.6	-
	3	0.60	1	3.89×10^3	-	-	–20.5	-
	Average	**1.03**	**1**	$\mathbf{3.83 \times 10^3}$	-	-	**–20.4**	-
	Std. Dev.	0.58	0	0.36×10^3	-	-	0.2	-
	95% C.I.	1.43	0	0.88×10^3 (23%)	-	-	0.6	-
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.26	6.5	5.09×10^3	616	3.14×10^6	–19.4	–17.6
	2	0.06	14	8.55×10^3	500	4.27×10^6	–20.7	–17.1
	3	0.08	7.5	6.20×10^3	335	2.08×10^6	–19.9	–16.1
	Average	**0.13**	**9.2**	$\mathbf{6.62 \times 10^3}$	**484**	$\mathbf{3.16 \times 10^6}$	**–20.0**	**–17.0**
	Std. Dev.	0.11	3.8	1.77×10^3	141	1.10×10^6	0.6	0.8
	95% C.I.	0.27	9.4	4.39×10^3 (66%)	351 (73%)	2.73×10^6	1.6	1.9
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	1.70	1.0	3.05×10^3	–5.47[b]	-[b]	–18.2	-[b]
	2	0.80	1.0	4.37×10^3	2.43	1.06×10^4	–19.0	–3.92
	3	0.60	1.0	3.97×10^3	1.06	4.20×10^3	–18.8	–1.86
	Average	**1.04**	**1.0**	$\mathbf{3.80 \times 10^3}$	**–0.66**[b]	-[b]	**–18.7**	-[b]
	Std. Dev.	0.58	0.0	0.67×10^3	4.22[b]	-[b]	0.5	-[b]
	95% C.I.	1.45	0.0	1.67×10^3 (44%)	10.49 (1586%)[b]	-[b]	1.1	-[b]
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.32	5.3	3.92×10^3	979	3.84×10^6	–18.8	–18.8
	2	0.24	3.4	4.84×10^3	1210	5.86×10^6	–19.3	–19.3
	3	0.26	2.3	3.99×10^3	997	3.98×10^6	–18.8	–18.8
	Average	**0.27**	**3.7**	$\mathbf{4.25 \times 10^3}$	**1060**	$\mathbf{4.56 \times 10^6}$	**–19.0**	**–19.0**
	Std. Dev.	0.04	1.5	0.51×10^3	130	1.13×10^6	0.3	0.3
	95% C.I.	0.10	3.7	1.28×10^3 (30%)	320 (30%)	2.80×10^6	0.7	0.7
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	12.9	0.1	4.97×10^4	1.24×10^4	6.19×10^8	–25.1	–25.1
	2	15.4	0.1	5.81×10^4	1.45×10^4	8.43×10^8	–25.5	–25.5
	3	14.7	0.04	4.95×10^4	1.24×10^4	6.12×10^8	–25.1	–25.1
	Average	**14.3**	**0.1**	$\mathbf{5.24 \times 10^4}$	$\mathbf{1.31 \times 10^4}$	$\mathbf{6.91 \times 10^8}$	**–25.2**	**–25.2**
	Std. Dev.	1.3	0.05	0.49×10^4	0.12×10^4	1.31×10^8	0.2	0.2
	95% C.I.	3.2	0.12	1.21×10^4 (23%)	0.30×10^4 (23%)	3.27×10^8	0.6	0.6

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b]Negative association constant obtained, hence calculation for β_{12} and ΔG are excluded.

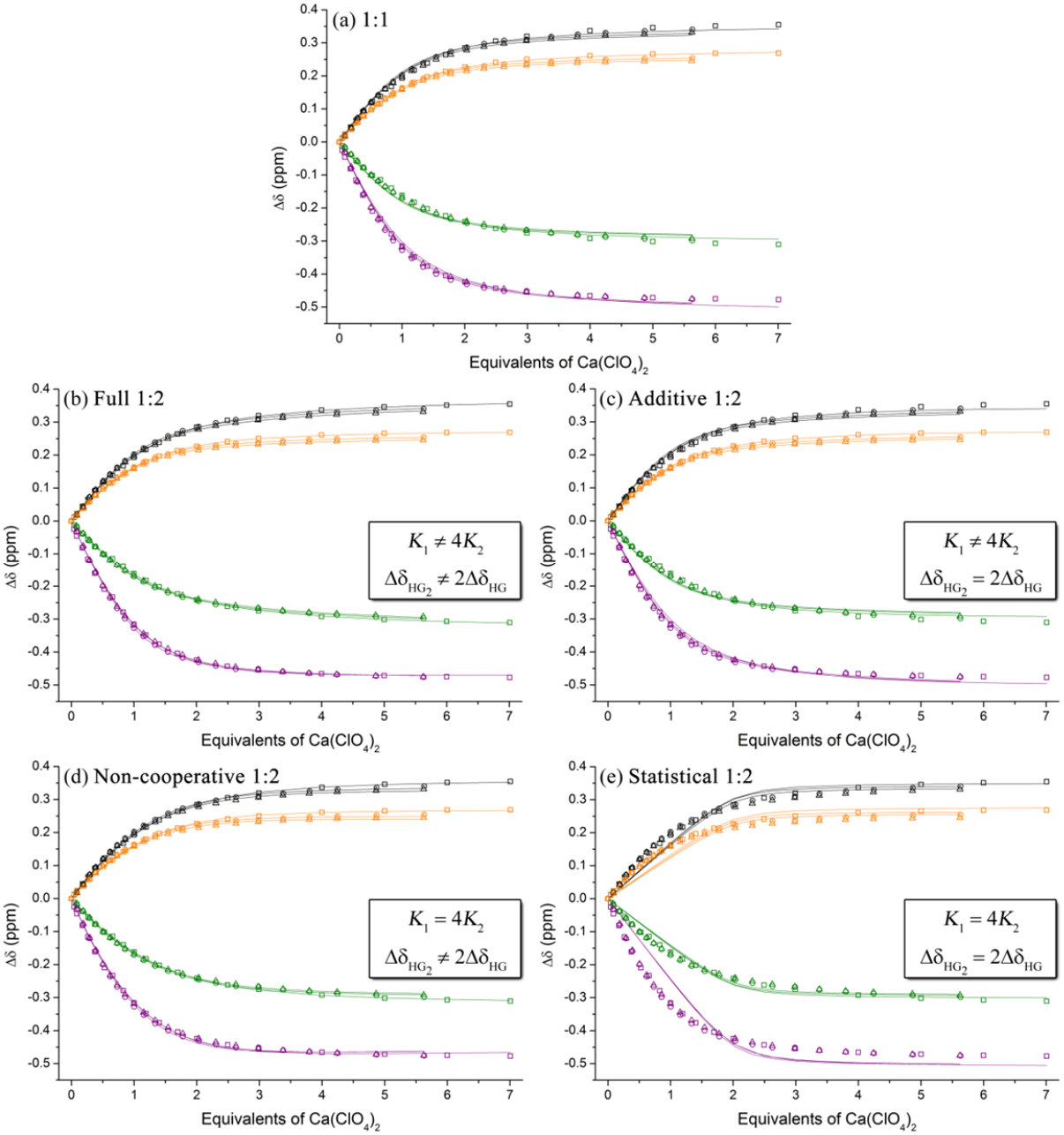


Figure S22. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $Ca(ClO_4)_2$ in $CDCl_3/CD_3OD$ (9:1, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 1:2** and **non-cooperative 1:2** model can describe this data much better than the other three models. We conclude therefore that the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best.

Table S20. Association constants of host 1 towards the sodium cation obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $NaClO_4$ in $CDCl_3/CD_3OD$ (9:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 5)	1	2.48	1	146	-	-	–12.3	-
	2	3.24	1	149	-	-	–12.4	-
	3	3.13	1	126	-	-	–12.0	-
	Average	**2.95**	**1**	**140**	-	-	**–12.2**	-
	Std. Dev.	0.41	0	12	-	-	0.2	-
	95% C.I.	1.02	0	31 (22%)	-	-	0.6	-
Full 2:1[b] (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta H_2G} \neq 2\delta_{\Delta HG}$)	1	0.25	9.9	317[b]	–366[b,c]	-[b,c]	–12.6	-[b,c]
	2	0.08	41	381[b]	–385[b,c]	-[b,c]	–13.0	-[b,c]
	3	0.28	11	342[b]	–353[b,c]	-[b,c]	–12.7	-[b,c]
	Average	**0.20**	**21**	**347**[b]	**–368**[b,c]	-[b,c]	**–12.8**	-[b,c]
	Std. Dev.	0.11	17	33[b]	16[b,c]	-[b,c]	0.2	-[b,c]
	95% C.I.	0.26	43	81 (23%)[b]	40 (11%)[b,c]	-[b,c]	0.6	-[b,c]
Full 1:2 (n-df = 10) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.24	10	196	321	6.31×10^4	–11.4	–16.0
	2	0.10	32	275	436	12.0×10^4	–12.2	–16.8
	3	0.26	12	200	378	7.57×10^4	–11.4	–16.4
	Average	**0.20**	**18**	**224**	**379**	$\mathbf{8.63 \times 10^4}$	**–11.7**	**–16.4**
	Std. Dev.	0.09	12	44	57	2.99×10^4	0.5	0.4
	95% C.I.	0.22	31	110 (49%)	143 (38%)	7.42×10^4	1.2	0.9
Additive 1:2 (n-df = 6) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.44	5.6	234	314	4.39×10^4	–11.8	–16.0
	2	0.30	11	170	506	3.02×10^4	–11.0	–17.1
	3	0.45	7.0	161	405	4.53×10^4	–10.9	–16.6
	Average	**0.40**	**7.8**	**188**	**409**	$\mathbf{3.98 \times 10^4}$	**–11.2**	**–16.6**
	Std. Dev.	0.08	2.7	40	96	0.84×10^4	0.5	0.6
	95% C.I.	0.21	6.7	99 (52%)	239 (58%)	2.08×10^4	1.2	1.5
Non-cooperative 1:2 (n-df = 9) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.33	7.5	997	249	2.49×10^5	–15.4	–15.4
	2	0.19	17	1220	305	3.71×10^5	–15.9	–15.9
	3	0.35	8.9	1020	255	2.59×10^5	–15.4	–15.4
	Average	**0.29**	**11**	**1080**	**270**	$\mathbf{2.93 \times 10^5}$	**–15.6**	**–15.6**
	Std. Dev.	0.09	5.1	120	31	0.68×10^5	0.3	0.3
	95% C.I.	0.22	13	300 (28%)	76 (28%)	1.69×10^5	0.7	0.7
Statistical 1:2 (n-df = 5) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	2.10	1.2	346	86.6	3.00×10^4	–12.8	–12.8
	2	2.90	1.1	356	89.0	3.17×10^4	–12.8	–12.8
	3	2.80	1.1	295	73.8	2.18×10^4	–12.4	–12.4
	Average	**2.60**	**1.1**	**332**	**83.1**	$\mathbf{2.78 \times 10^4}$	**–12.7**	**–12.7**
	Std. Dev.	0.44	0.04	33	8.2	0.53×10^4	0.3	0.3
	95% C.I.	1.08	0.1	81 (24%)	20.3 (24%)	1.32×10^4	0.6	0.6

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.
[b] Here K_1 is for the formaton of H:G complex and K_2 the association constant for the formation of the H_2G complex in the 2:1 equilibria.
[c] Negative association constant obtained, hence calculation for β_{21} and ΔG are excluded

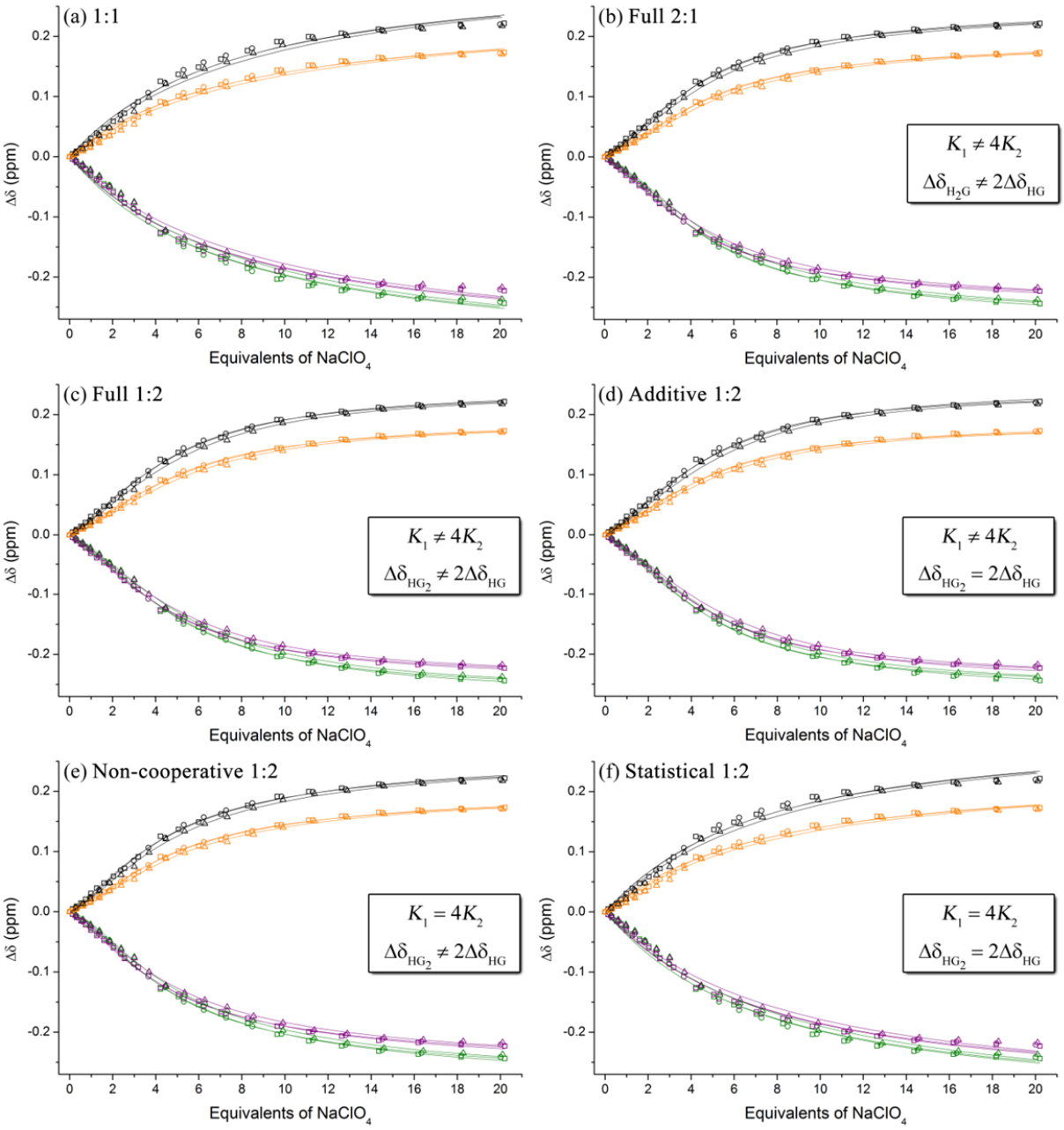


Figure S23. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $NaClO_4$ in $CDCl_3/CD_3OD$ (9:1, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △), ethylene-He (□, ○, △), aromatic-H3 (□, ○, △) and aromatic-H4 (□, ○, △); symbols indicate the order of the triplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to six different binding models: (a) **1:1**, (b) **full 2:1**, (c) **full 1:2**, (d) **additive 1:2** (e) **non-cooperative 1:2** and (f) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 2:1**, **full 1:2** and **non-cooperative 1:2** model can describe this data better than the **additive 1:2** and the **1:1** model. The **full 2:1** model does though show a negative K_2 for all the experiments. We conclude therefore that the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best, noting that the **full 2:1** needs also to be mentioned since the difficulty with K_2 in the **full 2:1** model may have to do with the inherent difficulty in detecting the formation of the 2:1 complex (only present at low guest concentration)..

7. Data Analysis for Cooperative Binding Studies in $CDCl_3/CD_3OD$ (9:1, v/v)

From the NMR titration of host **1** with $CaCl_2$, three different proton resonances (ethylene-Hd, ethylene-He and aromatic-H1) were recorded at every titration point, providing three sets of data for the binding models fitting analysis. From the NMR titration with TBA-Cl in the presence of $Ca(ClO_4)_2$, the three different proton resonances recorded at every titration point are aromatic-H1, aromatic-H3 and aromatic-H4, providing three sets of data for the binding models fitting analysis. Herein, the results from fitting to the **1:1** and all the four expressions of 1:2 binding models, i.e., **full 1:2**, **additive 1:2**, **non-cooperative 1:2** and **statistical 1:2** are reported.

Table S21. Association constants of host 1 binding simultaneously towards $CaCl_2$ ion-triplet obtained from ^1H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) with $CaCl_2$ in $CDCl_3/CD_3OD$ (9:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 4)	1	0.63	1	132	-	-	–12.1	-
	2	0.49	1	108	-	-	–11.6	-
	3	0.68	1	119	-	-	–11.8	-
	4	0.93	1	156	-	-	–12.5	-
	Average	**0.68**	**1**	**129**	-	-	**–12.0**	-
	Std. Dev.	0.18	0	21	-	-	0.4	-
	95% C.I.	0.29	0	33 (26%)	-	-	0.6	-
Full 1:2 (n-df = 8) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.02	32	201	62.3	1.25×10^4	–11.4	–12.0
	2	0.02	25	181	47.1	0.854×10^4	–11.2	–11.3
	3	0.03	23	178	43.1	0.767×10^4	–11.1	–11.0
	4	0.07	13	275	45.8	1.26×10^4	–12.2	–11.2
	Average	**0.03**	**23**	**209**	**49.6**	$\mathbf{1.03 \times 10^4}$	**–11.5**	**–11.4**
	Std. Dev.	0.02	7.5	45	8.6	0.26×10^4	0.5	0.4
	95% C.I.	0.03	12	72 (35%)	13.7 (28%)	0.41×10^4	0.8	0.6
Additive 1:2 (n-df = 5) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.44	1.4	289	84.0	2.42×10^4	–12.3	–12.7
	2	0.46	1.1	236	60.2	1.42×10^4	–11.8	–11.9
	3	0.65	1.0	263	65.7	1.73×10^4	–12.1	–12.1
	4	0.86	1.1	373	66.3	2.47×10^4	–13.0	–12.1
	Average	**0.60**	**1.2**	**290**	**69.1**	$\mathbf{2.01 \times 10^4}$	**–12.3**	**–12.2**
	Std. Dev.	0.20	0.2	59	10.3	0.52×10^4	0.5	0.4
	95% C.I.	0.31	0.3	95 (33%)	16.4 (24%)	0.83×10^4	0.8	0.6
Non-cooperative 1:2 (n-df = 7) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	0.03	21	156	38.9	0.607×10^4	–10.8	–10.8
	2	0.02	25	168	42.0	0.705×10^4	–11.0	–11.0
	3	0.03	23	184	46.1	0.851×10^4	–11.2	–11.2
	4	0.28	3.3	286	71.4	2.04×10^4	–12.3	–12.3
	Average	**0.09**	**18**	**198**	**49.6**	$\mathbf{1.05 \times 10^4}$	**–11.3**	**–11.3**
	Std. Dev.	0.13	9.8	59	14.8	0.67×10^4	0.7	0.7
	95% C.I.	0.20	16	94 (48%)	23.6 (48%)	1.06×10^4	1.1	1.1
Statistical 1:2 (n-df = 4) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	0.49	1.3	297	74.2	2.20×10^4	–12.4	–12.4
	2	47.1	0.01	4.62×10^{-4}	1.16×10^{-4}	5.34×10^{-8}	20.7	20.7
	3	0.65	1.0	263	65.7	1.73×10^4	–12.1	–12.1
	4	1.10	0.8	351	87.7	3.08×10^4	–12.8	–12.8
	Average	**12.3**	**0.8**	**228**	**56.9**	$\mathbf{1.75 \times 10^4}$	**–4.13**	**–4.13**
	Std. Dev.	23.2	0.6	156	39.0	1.30×10^4	16.59	16.59
	95% C.I.	36.9	0.9	248 (109%)	62.1 (109%)	2.06×10^4	26.40	26.40

[a] cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

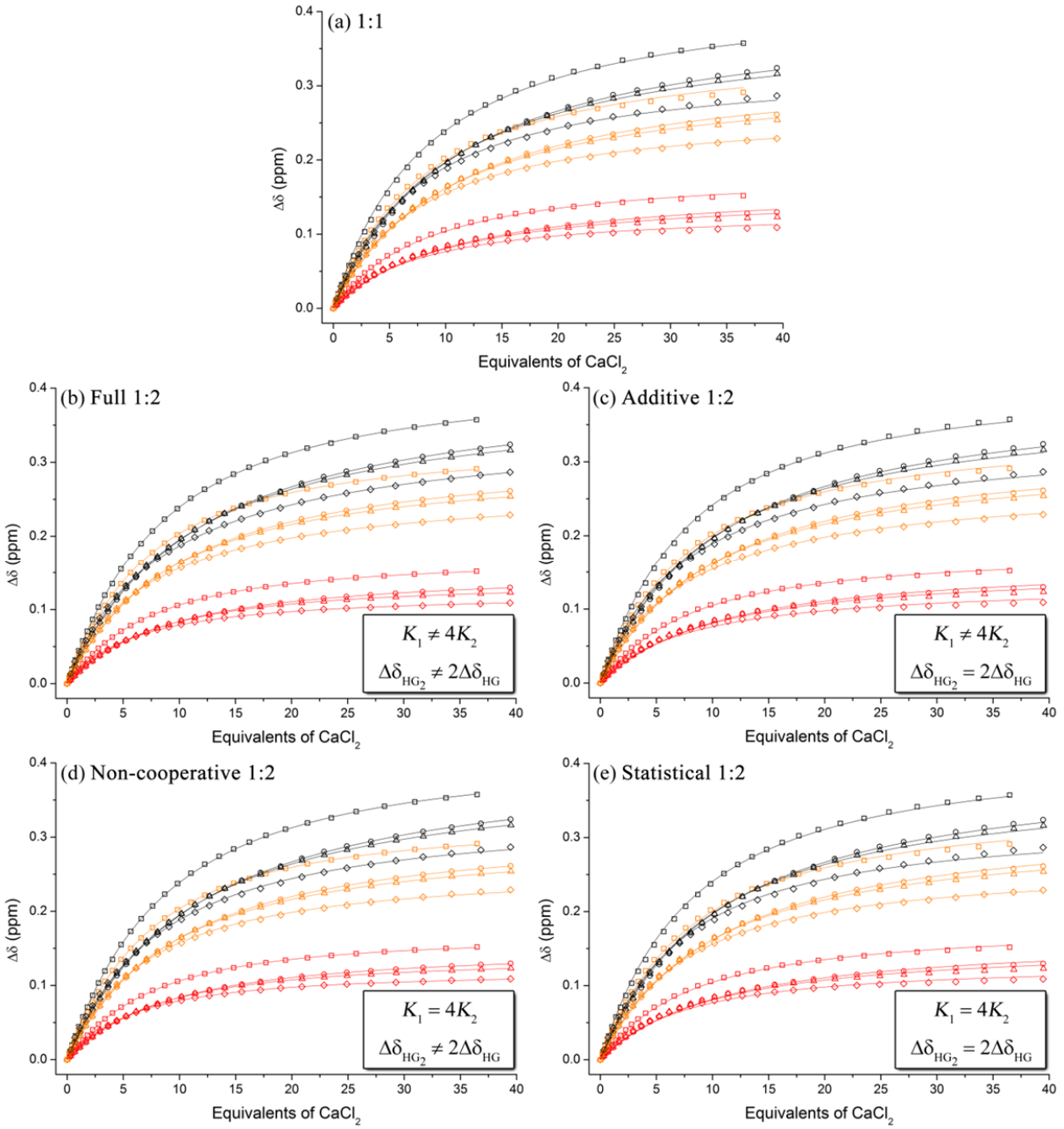


Figure S24. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) with $CaCl_2$ in $CDCl_3/CD_3OD$ (9:1, v/v), showing the change in chemical shifts (Δδ) for ethylene-Hd (□, ○, △, ◇), ethylene-He (□, ○, △, ◇), aromatic-H1 (□, ○, △, ◇), symbols indicate the order of the quadruplicatetriplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2** (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on both the cov_{fit} and inspection of the binding isotherms, the **full 1:2** and **non-cooperative 1:2** model can describe this data much better than the other three models. We conclude therefore that the **full 1:2** and **non-cooperative 1:2** binding model appear to fit the data best.

Table S22. Association constants of host 1 binding towards the chloride anion in the presence of 5 equivalent of the calcium dication obtained from ^{1}H NMR titrations (400 MHz, 298 K) of 1 (1.0 mM) + $Ca(ClO_4)_2$ (5.0 mM) with TBA-Cl in $CDCl_3/CD_3OD$ (9:1, v/v); and comparison of the binding models.

Binding model	Experiment #	cov_{fit} (10^{-3})	cov_{fit} factor[a]	K_1 (M^{-1})	K_2 (M^{-1})	β_{12} (M^{-2})	ΔG_1 (kJ mol^{-1})	ΔG_2 (kJ mol^{-1})
1:1 (n-df = 4)	1	42.6	1	34.9	-	-	–8.80	-
	2	43.3	1	54.2	-	-	–9.89	-
	3	46.0	1	57.6	-	-	–10.0	-
	4	49.3	1	60.3	-	-	–10.2	-
	Average	**45.3**	**1**	**51.7**	-	-	**–9.72**	-
	Std. Dev.	3.0	0	11.5	-	-	0.62	-
	95% C.I.	4.8	0	18.3 (35%)	-	-	0.99	-
Full 1:2 (n-df = 8) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	4.96	8.6	7.01×10^{-5}	1.46×10^{8}	1.03×10^{4}	25.4	–48.3
	2	14.6	3.0	7.76×10^{-5}	1.79×10^{8}	1.39×10^{4}	25.2	–48.8
	3	3.70	12	7.95×10^{-5}	1.82×10^{8}	1.44×10^{4}	25.1	–48.8
	4	3.80	13	8.00×10^{-5}	1.90×10^{8}	1.52×10^{4}	25.1	–49.0
	Average	**6.76**	**9.2**	$\mathbf{7.68 \times 10^{-5}}$	$\mathbf{1.74 \times 10^{8}}$	$\mathbf{1.34 \times 10^{4}}$	**25.2**	**–48.7**
	Std. Dev.	5.24	4.6	0.46×10^{-5}	0.19×10^{8}	0.22×10^{4}	0.2	0.3
	95% C.I.	8.33	7.3	0.73×10^{-5} (10%)	0.31×10^{8} (18%)	0.35×10^{4}	0.2	0.5
Additive 1:2 (n-df = 5) ($K_1 \neq 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	29.6	1.4	12.5	1480	1.85×10^{4}	–4.54	–19.8
	2	39.0	1.1	12.3	2010	2.47×10^{4}	–4.50	–20.6
	3	32.2	1.4	9.14	2870	2.63×10^{4}	–3.76	–21.4
	4	34.6	1.4	3.77	7230	2.73×10^{4}	–1.57	–23.7
	Average	**33.8**	**1.4**	**9.43**	**3400**	$\mathbf{2.42 \times 10^{4}}$	**–3.59**	**–21.4**
	Std. Dev.	4.0	0.2	4.08	2620	0.39×10^{4}	1.40	1.7
	95% C.I.	6.3	0.3	6.49 (69%)	4170 (123%)	0.62×10^{4}	2.22	2.7
Non-cooperative 1:2 (n-df = 7) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} \neq 2\delta_{\Delta HG}$)	1	13.5	3.2	355	88.7	3.15×10^{4}	–12.8	–12.8
	2	12.8	3.4	463	116	5.37×10^{4}	–13.5	–13.5
	3	13.1	3.5	475	119	5.64×10^{4}	–13.6	–13.6
	4	13.8	3.6	490	123	6.01×10^{4}	–13.6	–13.6
	Average	**13.3**	**3.4**	**446**	**111**	$\mathbf{5.04 \times 10^{4}}$	**–13.4**	**–13.4**
	Std. Dev.	0.5	0.2	62	15	1.29×10^{4}	0.4	0.4
	95% C.I.	0.7	0.3	98 (22%)	25 (22%)	2.05×10^{4}	0.6	0.6
Statistical 1:2 (n-df = 4) ($K_1 = 4K_2$) ($\delta_{\Delta HG_2} = 2\delta_{\Delta HG}$)	1	42.4	1.0	74.0	18.5	1370	–8.95	–8.95
	2	47.1	0.9	118	29.4	3450	–10.1	–10.1
	3	45.6	1.0	125	31.3	3930	–10.3	–10.3
	4	48.9	1.0	132	32.9	4330	–10.4	–10.4
	Average	**46.0**	**1.0**	**112**	**28.0**	**3270**	**–9.92**	**–9.92**
	Std. Dev.	2.8	0.04	26	6.5	1320	0.66	0.66
	95% C.I.	4.4	0.1	41 (37%)	10.4 (37%)	2090	1.04	1.04

[a]cov_{fit} factor = cov_{fit} for the **1:1** model divided by the cov_{fit} for the binding model under study.

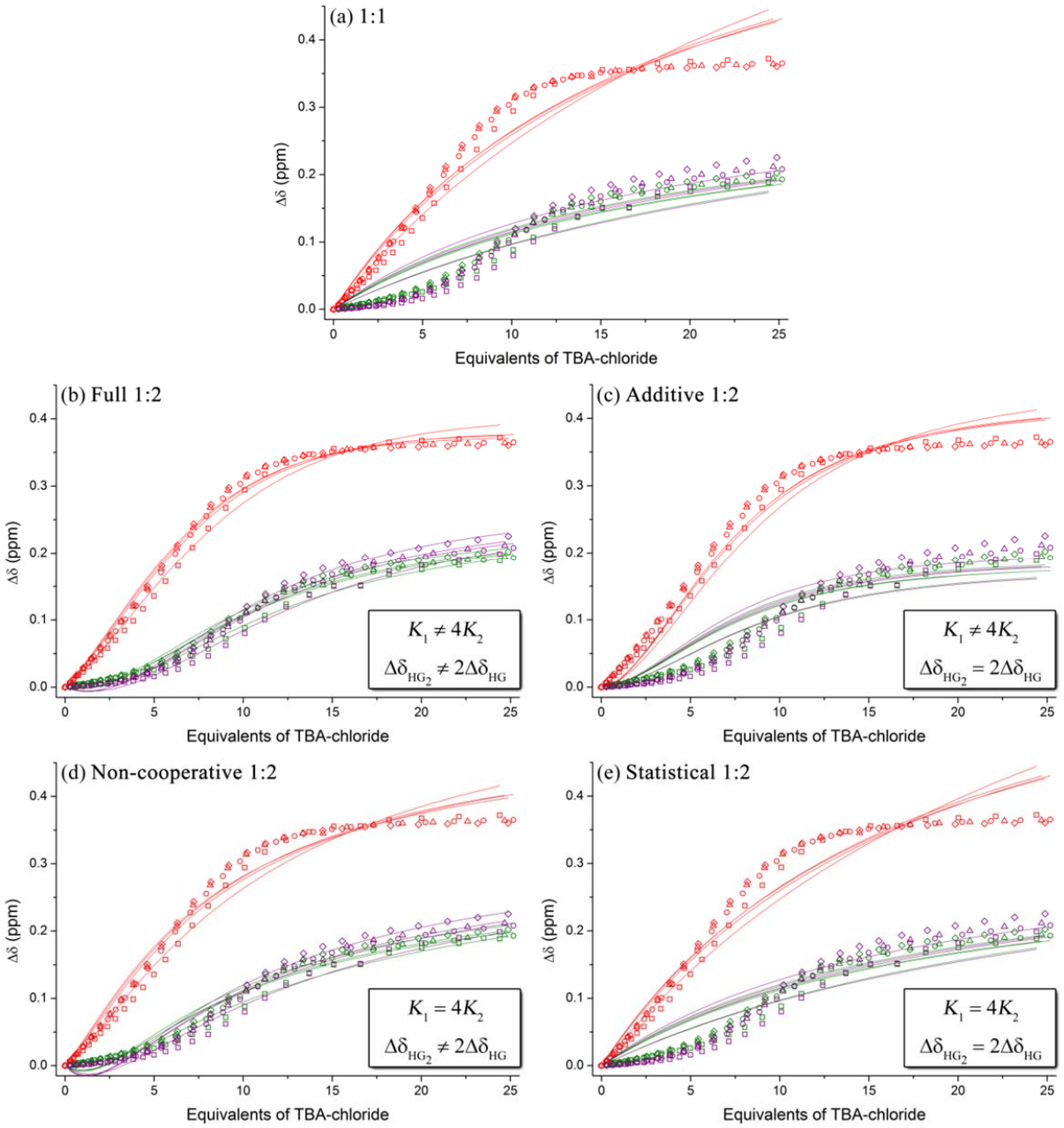


Figure S25. ^{1}H NMR titration (400 MHz, 298 K) of host **1** (1.0 mM) in the presence of $Ca(ClO_4)_2$ (5.0 equiv.) with TBA-chloride in $CDCl_3/CD_3OD$ (9:1, v/v), showing the change in chemical shifts (Δδ) for aromatic-H1 (□, ○, △, ◇), aromatic-H3 (□, ○, △, ◇) and aromatic-H4 (□, ○, △, ◇); symbols indicate the order of the quadruplicate measurements respectively. Also shown are the calculated binding isotherms (—) obtained by fitting with non-linear regression to five different binding models: (a) **1:1**, (b) **full 1:2**, (c) **additive 1:2**, (d) **non-cooperative 1:2** and (e) **statistical 1:2**.

Conclusion: Based on the cov_{fit} and inspection of the binding isotherms alone, the **full 1:2** and **non-cooperative 1:2** model appear to describe the data best. The K_1 for the **full 1:2** is unreasonably low and the K_2 unreasonably high. The **additive 1:2** model, although overall worse than both the **full 1:2** and **non-cooperative 1:2** does give useful indication of what the association constants might be if cooperativity is assumed. Therefore we conclude that the **non-cooperative 1:2** binding model appear to fit the data best but that the **additive 1:2** model should also be considered as a proxy for the **full 1:2** model.

8. Supplementary NMR Titration Spectra and Titration Isotherms

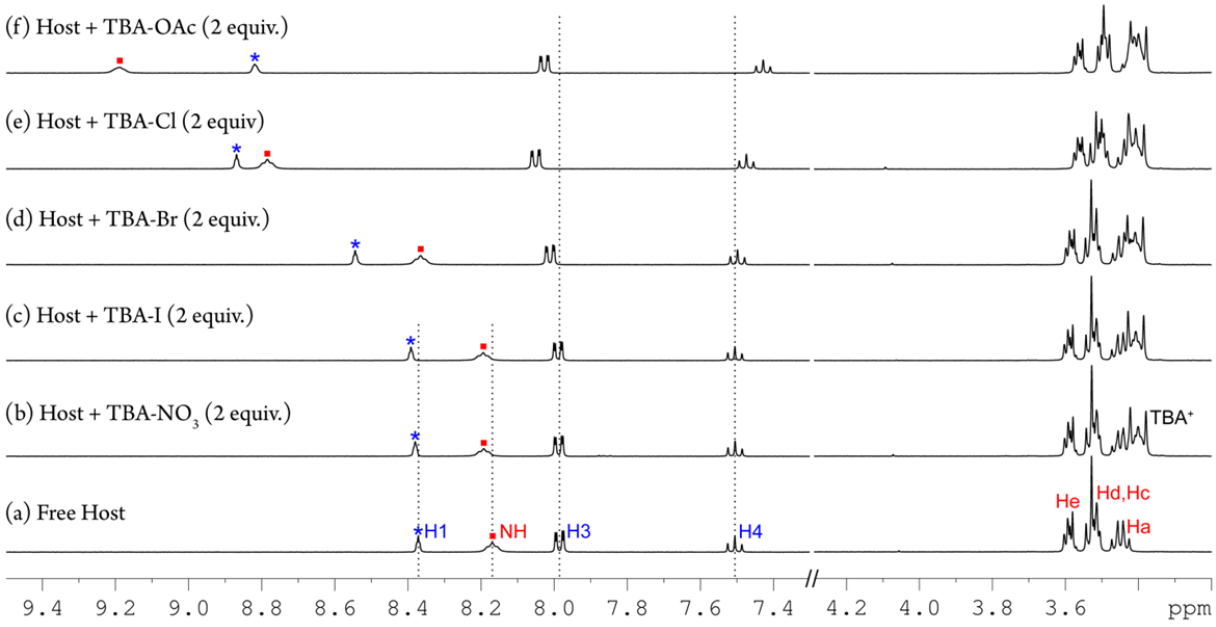


Figure S26. Partial ^{1}H NMR spectra (400 MHz, 298 K) of anion binding titration studies in DMSO-d_6/acetone-d_6 (1:9, v/v) of (a) host **1** (1.0 mM), (b) **1** titrated with TBA-nitrate (2.0 equiv.), (c) **1** titrated with TBA-iodide (2.0 equiv.), (d) **1** titrated with TBA-bromide (2.0 equiv.), (e) **1** titrated with TBA-chloride (2.0 equiv.), (f) **1** titrated with TBA-acetate (2.0 equiv.). Vertical dotted line demarking the original chemical shift.

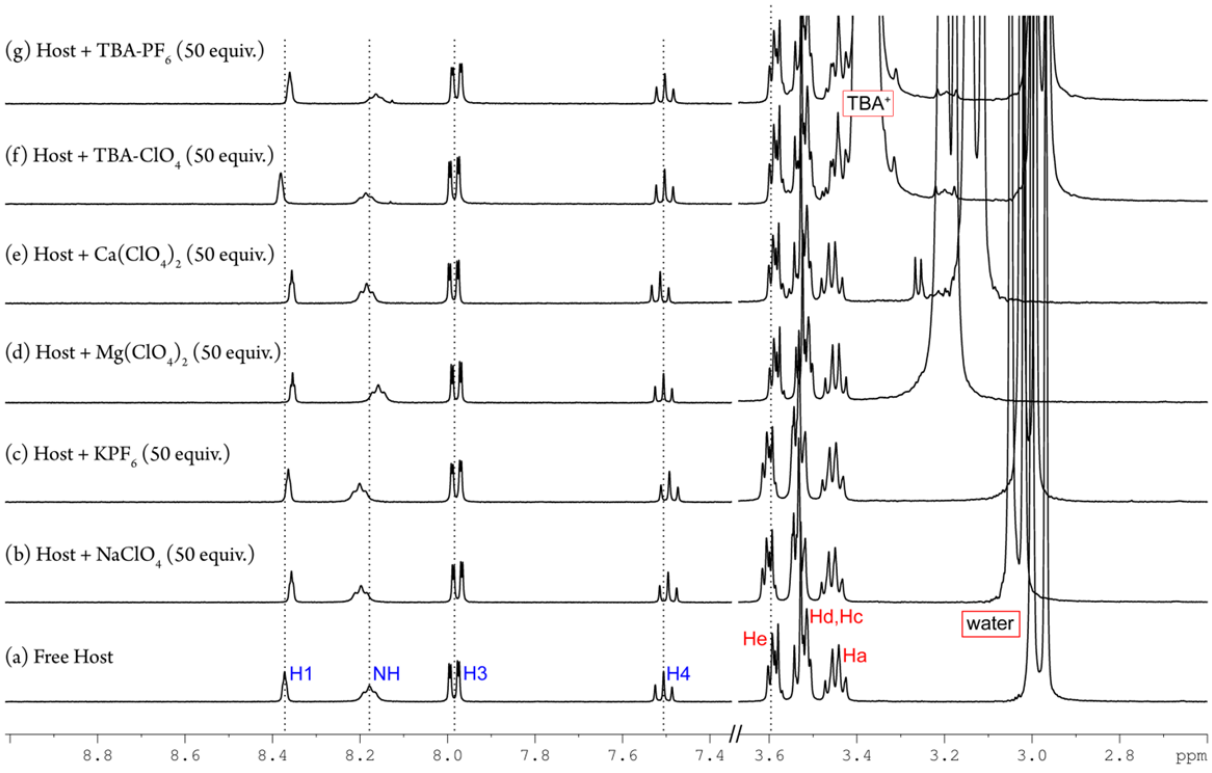


Figure S27. Partial ^{1}H NMR spectra (400 MHz, 298 K) of cation binding titration studies and control in DMSO-d_6/acetone-d_6 (1:9, v/v) of (a) host **1** (1.0 mM), (b) **1** titrated with sodium perchlorate (50 equiv.), (c) **1** titrated with potassium hexafluorophosphate (50 equiv.), (d) **1** titrated with magnesium perchlorate (50 equiv.), (e) **1** titrated with calcium perchlorate (50 equiv.), (f) **1** titrated with TBA-perchlorate (50 equiv.), (g) **1** titrated with TBA-hexafluorophosphate (50 equiv.). Vertical dotted line demarking the original chemical shift. In (d) and (e), the presence of more perchlorate anion resulted in a more drastic downfield of the water residual signals.

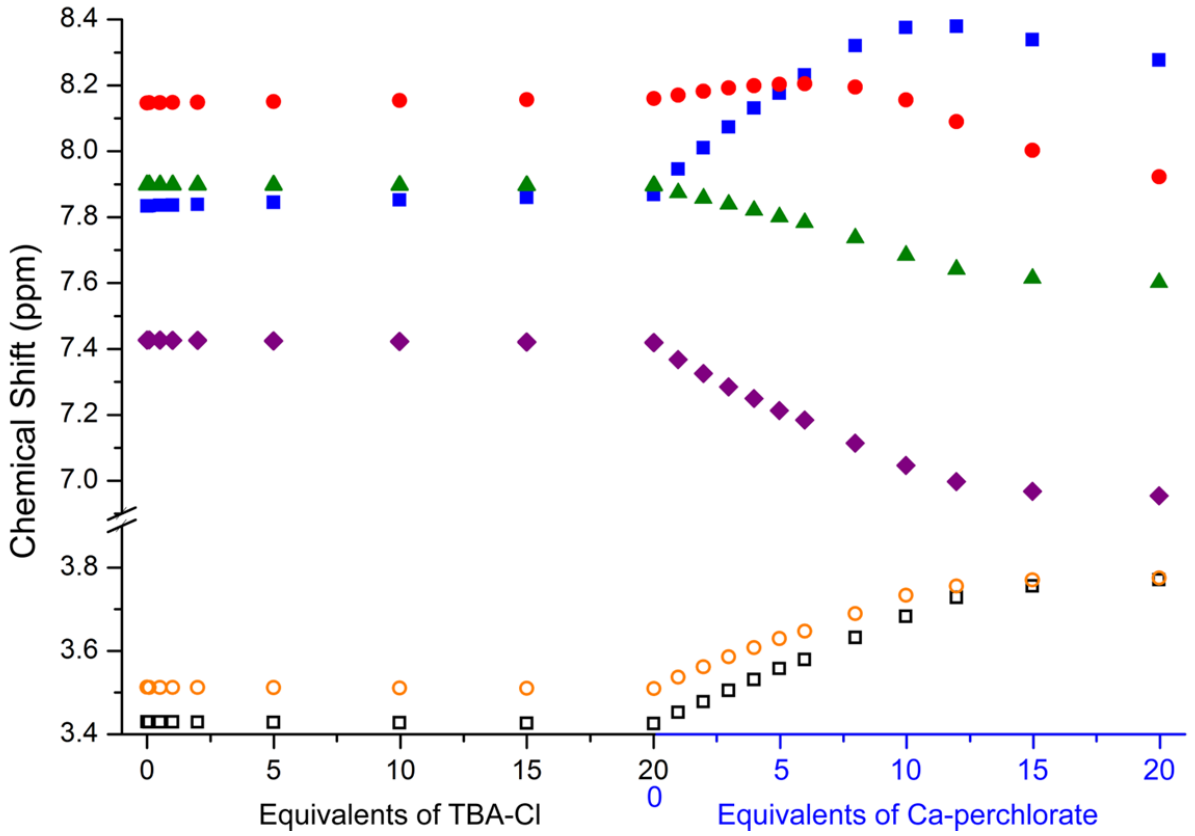


Figure S28. Isotherm for the ^{1}H NMR titration (400 MHz, 298 K) in CDCl3/CD3OD (9:1, v/v) of host **1** (1.0 mM) with TBA-chloride (up to 20 equiv.) showing no change in chemical shift (anion binding inhibited). Followed by titrating with calcium perchlorate (up to 20 equiv. to the host concentration), showing the change in chemical shifts for ethylene-Hd (□), ethylene-He (○), amide-H (■), aromatic-H1 (●), aromatic-H3 (▲) and aromatic-H4 (◆), indicating binding towards for calcium cation and chloride anion (switch "on") simultaneously. The concentration of TBA-chloride is diluted as calcium perchlorate is added, therefore resulting in upfield shifts (downward drop in the isotherm) for amide-H (■), aromatic-H1 (●) from approximately 10 equivalents of calcium perchlorate. The resulting final concentration of TBA-chloride at 20 equivalents of calcium perchlorate is diluted to 12.5 equivalents to the host.

9. Two-Dimensional NOESY $^{1}H–^{1}H$ NMR Studies

Sample of the macrocyclic host **1** (1.0 mM) was prepared in the same manner as described above for NMR titration binding studies, dissolved in a deuterated solvent mixture of $CDCl_3/CD_3OD$ (9:1, v/v). Measurements were carried out for the free host **1**, and with the presence of calcium diperchlorate tetrahydrate salt at three different equivalents (1.0, 2.0 and 5.0 equiv.) with respect to the host concentration. From the earlier NMR titration binding studies, using the association constants complex $K_1 = 6600\ M^{-1}$ and $K_2 = 484\ M^{-1}$ derived from the fit to the full 1:2 model, the percent formation of 1:1 **1**•Ca^{2+} complex was calculated at 1, 2 and 5 equivalents of $Ca(ClO_4)_2$ to be 58%, 63% and 39% respectively and that of the 1:2 complex **1**•$2Ca^{2+}$ at 1, 2 and 5 equivalents of $Ca(ClO_4)_2$ to be 7%, 25% and 59% respectively.[11, 21] Combined, this means that calculated percent saturation of **1** bound to $Ca(ClO_4)_2$ at 1, 2 and 5 equivalents was 63%, 74% and 98% respectively.

The 2–D NOESY NMR experiment was carried out on a Bruker Avance III 400 spectrometer operating at a frequency of 400.13 MHz with the probe temperature maintained at 298 K. Typically, the spectra were acquired with 32 scans, 800 ms mixing time, 1.5 s relaxation delay, 10.2 ppm spectral width and 512/256 (F1/F2) FID data points.

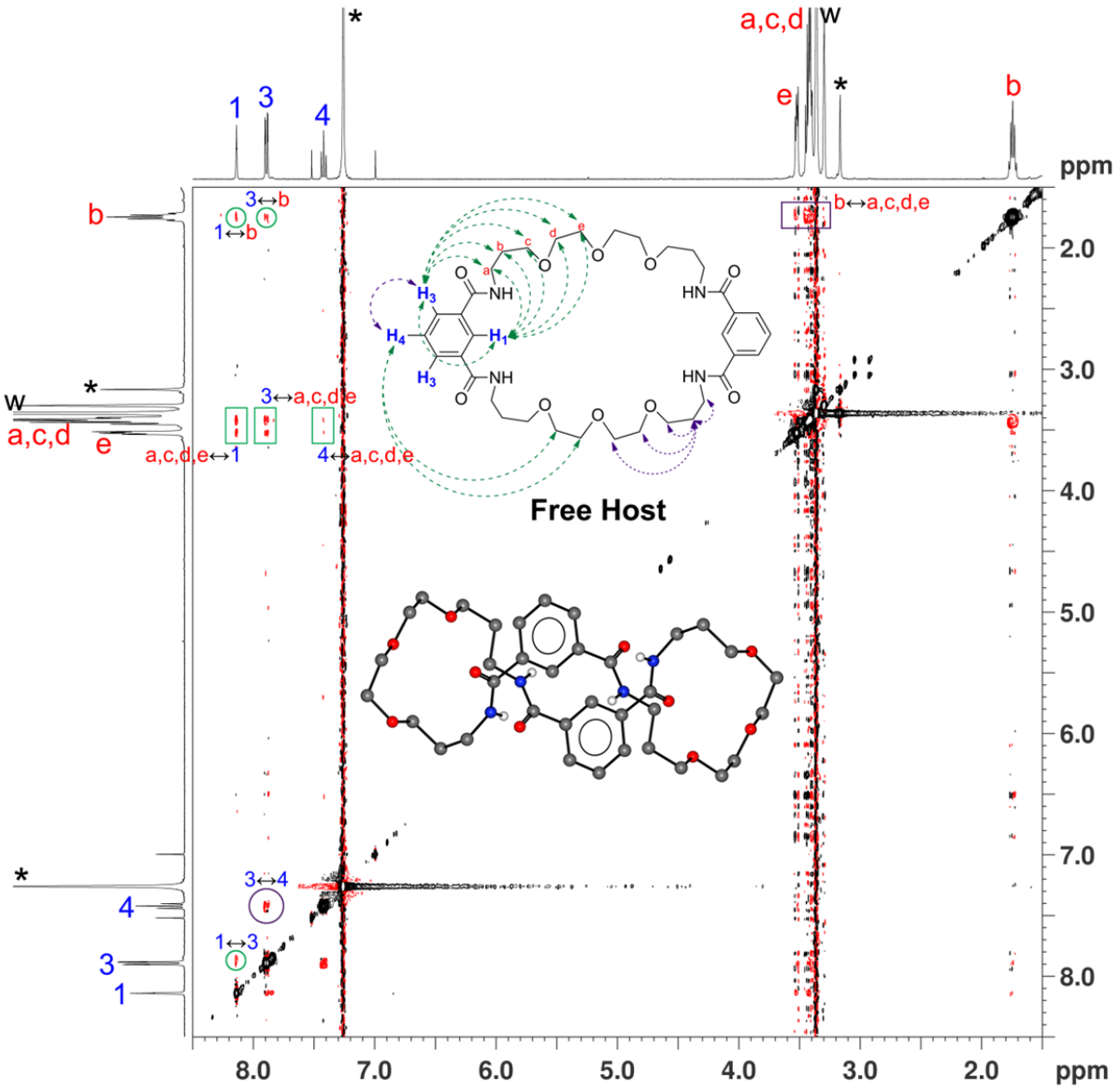


Figure S29. 2–D NOESY ^{1}H–^{1}H NMR (400 MHz, 298 K) spectrum of host **1** (1.0 mM) in $CDCl_3/CD_3OD$ (9:1, v/v), showing key distal intramolecular NOE cross-peaks (marked in green) suggesting folded-closed conformation of **1** consistent to the X-ray crystal structure. Insets: (top) drawn structure of **1** with the respective NOE interactions marked in green (distal) and purple (proximal); (bottom) X-ray crystal structure of **1**, all H atoms are omitted for clarity, except amide-H.

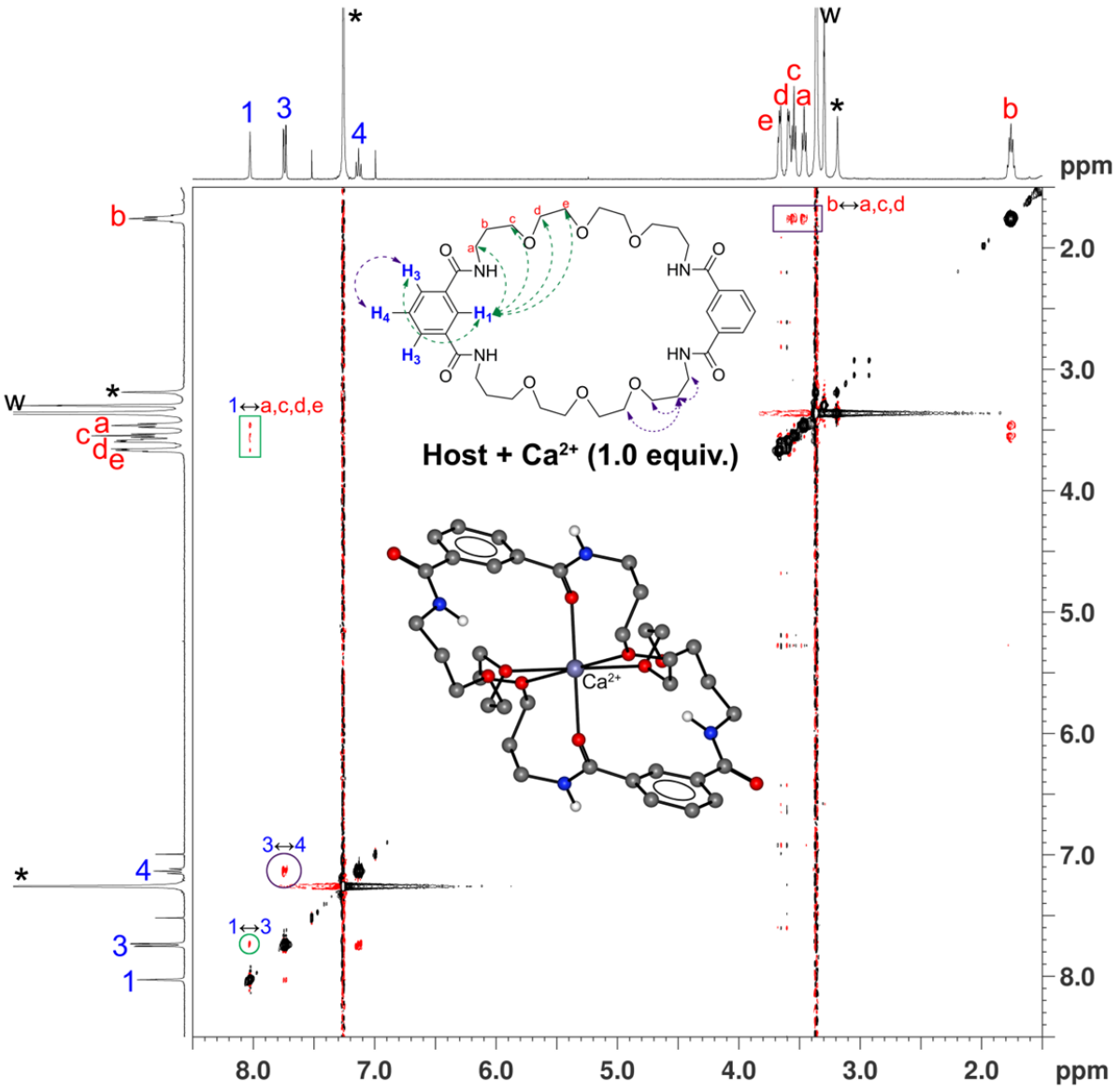


Figure S30. 2–D NOESY ^{1}H–^{1}H NMR (400 MHz, 298 K) spectrum of host **1** (1.0 mM) with $Ca(ClO_4)_2$ (1.0 equiv.) in $CDCl_3/CD_3OD$ (9:1, v/v), showing the remaining key distal intramolecular NOE cross-peaks (marked in green); suggesting structural perturbation of the folded-closed conformation of **1** as a result of the complexation to Ca^{2+}. At this point in the titration the calculated ratio of free **1**, **1**•Ca^{2+} and **1**•2Ca^{2+} is 35%, 58% and 7%, respectively. Inset: (top) drawn structure of **1** with the respective NOE interactions marked in green (distal) and purple (proximal); (bottom) DFT (PBE1PBE/6-31+G(d)) optimized structure of **1**•Ca^{2+} complex without counterions illustrating the anticipated 'opened' conformation, all H atoms are omitted for clarity, except amide-H.

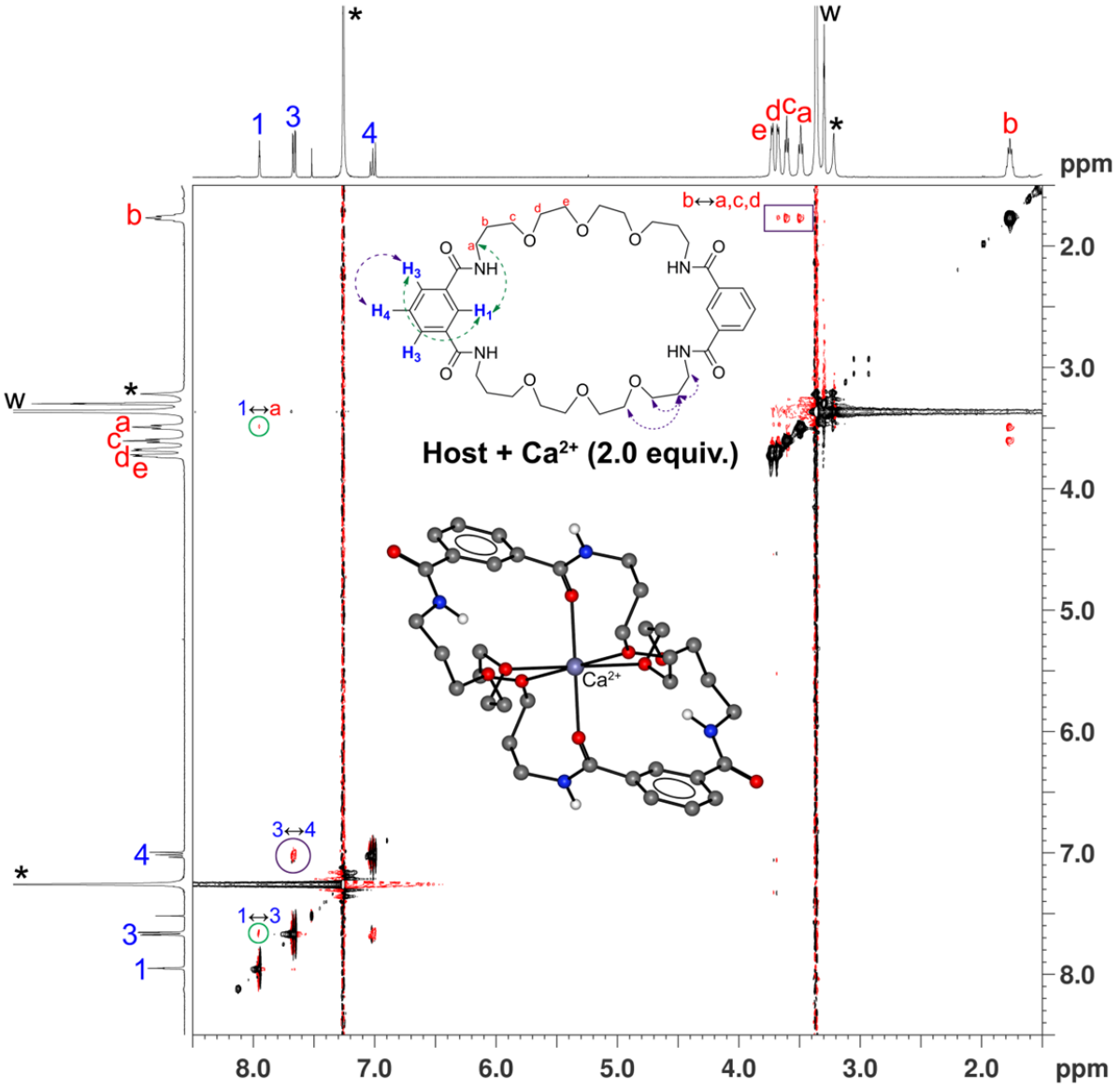


Figure S31. 2–D NOESY ^{1}H–^{1}H NMR (400 MHz, 298 K) spectrum of host **1** (1.0 mM) with $Ca(ClO_4)_2$ (2.0 equiv.) in $CDCl_3/CD_3OD$ (9:1, v/v), showing the remaining key distal intramolecular NOE cross-peaks (marked in green); suggesting structural perturbation of the folded-closed conformation of **1** as a result of the complexation to Ca^{2+}. At this point in the titration the calculated ratio of free **1**, **1**•Ca^{2+} and **1**•2Ca^{2+} is 12%, 63% and 25%, respectively. Inset: (top) drawn structure of **1** with the respective NOE interactions marked in green (distal) and purple (proximal); (bottom) DFT (PBE1PBE/6-31+G(d)) optimized structure of **1**•Ca^{2+} complex without counterions illustrating the anticipated 'opened' conformation, all H atoms are omitted for clarity, except amide-H.

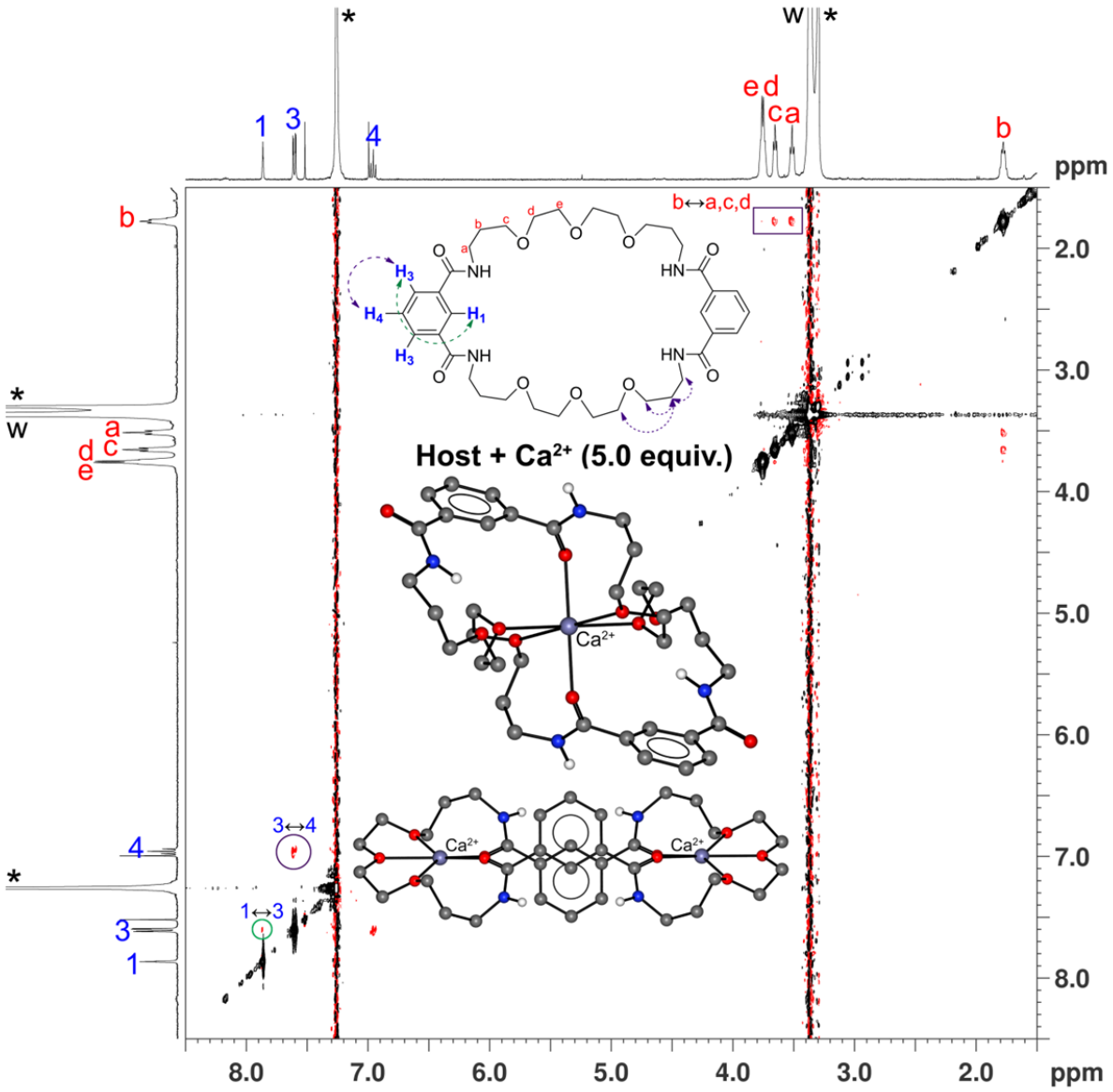


Figure S32. 2–D NOESY ^{1}H–^{1}H NMR (400 MHz, 298 K) spectrum of host **1** (1.0 mM) with $Ca(ClO_4)_2$ (5.0 equiv.) in $CDCl_3/CD_3OD$ (9:1, v/v), showing virtually no remaining distal intramolecular NOE cross-peaks (marked in green); suggesting structural perturbation of the folded-closed conformation of **1** as a result of the complexation to Ca^{2+}. At this point in the titration the calculated ratio of free **1**, **1**•Ca^{2+} and **1**•2Ca^{2+} is 2%, 39% and 59%, respectively. Inset: (top) drawn structure of **1** with the respective NOE interactions marked in green (distal) and purple (proximal); (bottom) DFT (PBE1PBE/6-31+G(d)) optimized structure of **1**•Ca^{2+} complex without counterions illustrating the anticipated 'opened' conformation and the X-ray crystal structure of **1**•2[$Ca(ClO_4)_2$]•4H_2O, all H atoms, counterions and water molecules are omitted for clarity, except amide-H.

10. Details of Computational Methods and Coordinates of Optimized Geometries

Methodology:

DFT calculations were performed using the Gaussian 09 software package,[22] revision B.01 for geometry optimization, revision D.01 for single point energy and frequency calculations, with the hybrid PBE1PBE[23] functional, running on 8-core Macpro workstations.

The input starting geometry for the quantum mechanics DFT calculation was obtained by taking the X-ray structure of the free host, adding a calcium atom at the center of the symmetrical host molecule, adding six dummy bonds from the crown-6-ether oxygen coordinated to Ca^{2+}, followed by performing a preliminary energy minimization using MM2 force field method. The resulting coordinates was exported with the dummy bonds removed for the geometry optimization using Gaussian 09.

The geometry of the host-guest complex was optimized at the PBE1PBE/6-31+G(d) level of theory, and all calculations were performed in vacuum and the default fine integration grid implemented in the Gaussian 09 software was employed throughout. The minimum energy structure for the complex was calculated without any symmetry constraints and were confirmed to be minima by calculating their normal vibrations using the same within the harmonic approximation and observing that there were no imaginary frequencies.

Coordinates of optimized geometry and calculation summary of host-gest complex:

Energy: –3048.873401 a.u.
Charge: 2
Spin: Singlet
Dipole Moment: 0.005 Debye
Point group: C1

H	-2.854037	3.841826	1.096631	H	-3.420351	0.856597	-2.299310
O	7.820990	0.563383	0.897541	C	-6.520649	2.601806	1.697319
O	-0.108249	0.493722	-2.415075	C	-7.166913	1.705306	0.649056
O	-4.162924	2.246197	1.267834	C	-6.690904	-0.441568	-0.451276
H	3.269844	3.409724	-1.980780	H	-7.401412	2.280788	-0.258625
H	2.178860	2.075959	-4.354838	C	2.235179	2.503501	-0.520335
H	4.438722	1.089023	-1.016880	C	-3.458950	-2.460214	-0.322404

C	-3.529541	-3.159142	-1.531803
O	-2.164720	1.079822	-0.653262
N	-6.290610	0.595600	0.324883
C	-4.502693	-1.621156	0.070117
C	-4.672681	-3.041403	-2.319642
C	-5.704477	-2.183702	-1.940534
N	2.369167	3.007193	-1.749884
O	-1.144967	-2.043964	0.103231
C	5.609301	1.442376	0.761098
N	6.290440	-0.595792	-0.324721
O	-7.820816	-0.563424	-0.897922
C	6.690955	0.441435	0.451233
N	-2.369015	-3.007343	1.750028
C	3.459030	2.460105	0.322595
C	4.672811	3.041202	2.319832
H	-5.305263	0.746490	0.499577
C	-5.609221	-1.442529	-0.760981
O	1.145001	2.044069	-0.103014
C	-1.369485	0.881006	-2.959099
C	-5.203985	3.236932	1.284505
H	0.354232	3.166061	-2.127896
H	-6.595396	-2.067872	-2.552073
C	4.502753	1.621043	-0.069967
H	-7.218384	3.416747	1.923634
H	-2.480852	-0.556813	-1.801559
O	4.162622	-2.245982	-1.268086
H	-6.370972	2.048390	2.633122
H	-4.924288	4.021808	2.000643
H	-4.438696	-1.089133	1.017029
C	-2.235092	-2.503540	0.520520
H	-2.178697	-2.076176	4.355005
C	-2.493969	2.472064	-0.500643
C	3.529655	3.158984	1.532021
H	0.465183	2.363441	-4.513465
H	-3.321322	2.718121	-1.177115
H	1.878433	0.312348	-2.715430
C	1.282212	3.155738	-2.704954
H	-2.160815	2.304900	1.618748
H	0.894793	-0.021087	-4.149838
H	6.595529	2.067666	2.552188
H	-1.387089	-4.138270	3.175205
C	-1.238011	-2.079507	3.789157
C	-1.014912	-0.657135	3.295046
C	1.369540	-0.880958	2.959252
H	5.292695	-3.698214	-0.289223
C	1.238159	2.079363	-3.789014
H	1.561869	-0.340148	3.896258
H	1.624319	-3.086056	0.769800
H	-1.624105	3.086144	-0.769489
H	-0.354060	-3.166117	2.127991
H	-0.464999	-2.363559	4.513581
C	6.520271	-2.601365	-1.698125
C	-1.282029	-3.155856	2.705070
H	-1.878419	-0.312516	2.715621
H	2.480820	0.556935	1.801726
H	1.369864	-1.956344	3.175361
C	2.436381	-0.526287	1.945753
H	-0.894802	0.020958	4.150037
H	2.853935	-3.841737	-1.096507
H	3.321587	-2.717849	1.177050
H	3.420395	-0.856442	2.299417
C	2.494065	-2.471902	0.500742
H	2.160442	-2.304929	-1.618607
C	2.894010	-2.755180	-0.934141
H	4.923875	-4.021254	-2.001851
H	6.370433	-2.047510	-2.633644
C	5.203688	-3.236706	-1.285397
C	7.166692	-1.705347	-0.649536
H	7.401317	-2.281242	0.257847
H	7.217980	-3.416190	-1.924941
H	-3.269652	-3.409971	1.980910
H	5.305064	-0.746592	-0.499280
O	2.164735	-1.079683	0.653391
H	1.387334	4.138134	-3.175113
C	-2.894191	2.755288	0.934170
H	2.713196	3.807925	1.839027
C	5.704598	2.183511	1.940671
H	-2.713065	-3.808079	-1.838771
O	0.108276	-0.493720	2.415257
C	1.014956	0.657021	-3.294866
H	8.116522	-1.306654	-1.018926
H	-4.755807	-3.615348	-3.238324
H	-1.561819	0.340189	-3.896100
H	-5.292820	3.697972	0.288098
H	4.755960	3.615111	3.238534
H	-8.116796	1.306787	1.018493
H	-1.369760	1.956390	-3.175224
C	-2.436361	0.526403	-1.945615
Ca	-0.000008	0.000059	0.000101

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