Supplementary Material (ESI) for Chemical Communications

Supplementary Material

A deuterated deep-cavity cavitand confirms the importance of C-H···X-R hydrogen bonds in guest binding

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Experimental

General

Resorcinol, pyridine and CuO were purchased from Aldrich Chemical Company. All deuterated solvents and reactants were purchased from Cambridge Isotopes. Pyridine and DMF were stored over molecular sieves (3Å). Ether was distilled from a Na/benzophenone still. Other reagents were used as received. All reactions were run under a nitrogen atmosphere.

Flash chromatography (Silica gel 60 Å, 200–400 mesh; Natland International) was used for product purification. ^{1}H NMR spectra were recorded on a Varian Unity Inova instrument (500 MHz). MS analysis was performed with a PerSeptive Biosystems Voyager Elite MALDI-TOF instrument.

Synthesis and Characterization of deuterated 3,5-dibromobenzalaldehyde (4)

To an oven-dried round bottom flask containing 8.1g (25 mmol) of 1,3,5-tribromobenzene was added 250 mL ether. This solution was cooled to -78°C and 10.3 mL of 2.5 M *n*-BuLi was added drop-wise. Subsequently, 2.0 mL of d_7-DMF was added to the reaction mixture drop-wise and the reaction was allowed to stir at –78 °C for 1.5 h. The solution was then removed from the dry ice/acetone bath and allowed to reach 0 °C. The reaction mixture was then acidified with excess 10% aqueous HCl and extracted three times with $CHCl_3$. The organic layers were combined and dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure leaving a white solid. The solid was then dissolved in $CHCl_3$ and a small amount of silica added to the solution. The solvent was removed under reduced pressure leaving free flowing silica. This was placed on a column prepared with 100% hexanes and the silica eluted with hexanes to remove starting material. The mobile phase was changed to 50% $CHCl_3$/hexanes to elute product **4**. Removal of the solvent under reduced pressure gave the pure product as a white solid in 69% yield (4.52 g, 17.1 mmol). With the exception of the absence of the benzal C-H signal, the NMR was identical to the previously reported protio derivative (Xi, H.; Gibb, C. L. D.; Gibb, B. C., *J. Org. Chem.,* **1999**, 64, 9286-9288).

Synthesis and Characterization of deuterated dibromobenzal bromide (5)

To an oven-dried round bottom flask containing 4.52 g (17.1 mmol) of **4** was added 200 mL dichloromethane. This solution was then transferred to a glove box to inject 12.5 mL BBr_3 (18.8 mmol). This solution was then allowed to stir at room temperature for 3 d. The reaction solution was then poured onto a column prepared with 100% hexanes and the product eluted with hexanes. The solution containing the product was then removed by reduced pressure leaving a white crystalline solid. This solid was recrystallized from hexanes to produce **5** in an 84% yield (5.9 g, 14.4 mmol). With the exception of the absence of the benzal C-H signal, the NMR was identical to the previously reported protio derivative (Xi, H.; Gibb, C. L. D.; Gibb, B. C., *J. Org. Chem.,* **1999**, 64, 9286-9288).

Synthesis and Characterization of deep cavity cavitand (7)

To a dried round bottom flask was added 500 mg (0.55 mmol) of resorcinarene **6** and 1.35 g (3.3 mmol) **5**, 20 mL of DMSO-d_6 and molecular sieves. DBU (0.67g, 0.66 mL) was then injected into the solution. The reaction was heated to 80 °C for 5 d. After this time, the solution was cooled, the solvent removed under reduced pressure, and the crude product extracted three times with $CHCl_3$ and H_2O. The organic layer was collected, dried with Na_2SO_4, the salt filtered off, and the solvent removed under reduced pressure to give a red/brown oil. This was dissolved in $CHCl_3$ and a small amount of silica added. The solvent was removed under reduced pressure leaving free-flowing silica. This was loaded onto a column prepared with 100% hexanes. The column was eluted with hexanes to remove unreacted **5**. The mobile phase was then changed to 50% $CHCl_3$/hexanes to elute product **7** as a white solid (0.25 g, 33% yield, >90% deuterium incorporation). With the exception of a small benzal C-H signal, the NMR was identical to the previously reported protio derivative (Xi, H.; Gibb, C. L. D.; Gibb, B. C., *J. Org. Chem.,* **1999**, 64, 9286-9288).

Synthesis and Characterization of d_4-host (2)

To a dried round bottom flask was added 0.25g **7** (0.13 mmol), 0.18 g K_2CO_3 (1.6 mmol), 0.086 g resorcinol (0.78 mmol) and 25 mL pyridine. N_2 was then bubbled through the solution for 5 min. before 0.13 g CuO (1.6 mmol) was added. A reflux condenser was placed on the flask and the solution was heated to vigorous reflux (sand bath) for 7 d. After this time, the flask was cooled and the solvent removed under reduced pressure to leave a black solid. This was suspended in $CHCl_3$ and the crude product washed through a short silica plug with $CHCl_3$. The solvent was then removed under reduced pressure to leave a white solid. This was dissolved in $CHCl_3$ and a small amount of silica added. The solvent was removed under reduced pressure to leave free-flowing silica. This was loaded onto a column prepared with 50% $CHCl_3$/hexanes and eluted with the same. The product was collected and solvent removed under reduced pressure to give pure **2** (0.11g, 43% yield, >90% deuterium incorporation). With the exception of a small benzal C-H signal, the NMR was identical to the previously reported protio derivative **1** (Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C., *J. Am. Chem. Soc.*, **2001**, 123, 5849-5850).

Synthesis of Iodocycloheptane

Following a standard Feinkelstein procedure,1g bromocycloheptane (5.6 mmol 0.78 mL) and 2.52g NaI (16.8 mmol) were dissolved in 10 mL acetone. This was allowed to stir at rt for 2d. The resulting white precipitate was filtered off. The solution was then diluted with ether and washed with water then 10% aqueous sodium thiosulfate. The organic layer was then dried with Na_2SO_4 and decolorizing carbon added. The mixture was then filtered and the solvent removed under reduced pressure to give the pure guest as a clear oil (0.81g, 3.6 mmol, 65%). The NMR was identical to a previously reported sample (Montoro, R., Wirth, T.; Org. Lett. **2003**, 5, 4729-4731).

Synthesis of Iodocyclooctane

Following the procedure described by Olah *et al.* (Olah, G. A., Narang, S. C.; Gupta, B. G. B.; Malhotra, R.; *J. Org. Chem.*, **1979**, *44*, 1247) 2.0 g cyclooctanol (2.1

mL, 15.6 mmol) was dissolved in 15 mL CH_3CN. To this stirring solution was added 4.68 g NaI (31.2 mmol) and 3.39 g (3.99 mL, 31.2 mmol) TMSCl. The reaction was stirred for 4 h. After this time, the solution was diluted with 20 mL diethyl ether and the resultant solution washed with water and twice with 10% aqueous sodium thiosulfate. The organic layer was collected, dried with $NaSO_4$, filtered, and the solvent removed under reduced pressure to give the guest as an oily while solid (3.60g, 15.1 mmol, 97%). The NMR was identical to a previously reported sample (Barluenga, J.; Gonzalex-Bobes, F.; Gonzalesm J. M.; Angew. Chem. Int. Ed. **2002**, 41, 2556).

Binding Studies.

All quoted association constants (K, M^{-1}) were the average of at least three titrations (starting from fresh stock solution). For each experiment, a 1 mM stock solution of hosts **1** or **2** were prepared in DMSO-d_6. The concentration of the stock solutions of guests (in the range of 50 mM-250 mM) depended on the strength of binding; weaker binding guest solutions were of higher concentration (see *Comprehensive Supramolecular Chemistry*; Ed. Lehn, J.-M., Atwood, J. L., Davis, J. E. D., MacNicol, D. D., Vögtle, F., Pergamon: New York, **1996**; Volume 8, Chapter 10, Tsukube, H., "Determination of Stability Constants"). A 0.5 mL solution of host was then measured into an NMR tube and its spectra recorded (500 MHz NMR, 298 K). Small aliquots of guest solution were measured into the tube and the spectra recorded after each addition. The association constants were calculated according to the following equilibrium (see: Connors, K.A., *Binding Constants*; Wiley Interscience, New York, 1987):

$$H + G \rightleftharpoons HG$$

$$K_a = \frac{[HG]}{[H][G]}$$

While adamantane, cyanoadamantane and 2-bromoadamantane bound slowly on the (500 MHz) NMR time scale, the other guests were fastbinders and the determination of the K_a values necessitated titration experiments. Thus, the shifts of the various proton signals were recorded after each addition of guest to generate a binding isotherm.

Non-linear regression using Origin 6.1 (Aston Scientific Ltd.) was used to generate the association constants K_a according to the equation:

$$\Delta = \frac{\frac{\Delta_{11}}{2}}{K[G] - 1 - K[H] + \sqrt{\left(1 + K[H] - K[G]\right)^2 + 4K[G]}} + 1$$

where Δ = the peak shift in Hz, Δ_{11} = the maximum peak shift in Hz, [G] = the concentration of guest, and [H] = concentration of host which is treated as a constant. Examples of titration curves of all the fast binding guests are shown below (Figures S1-S18)

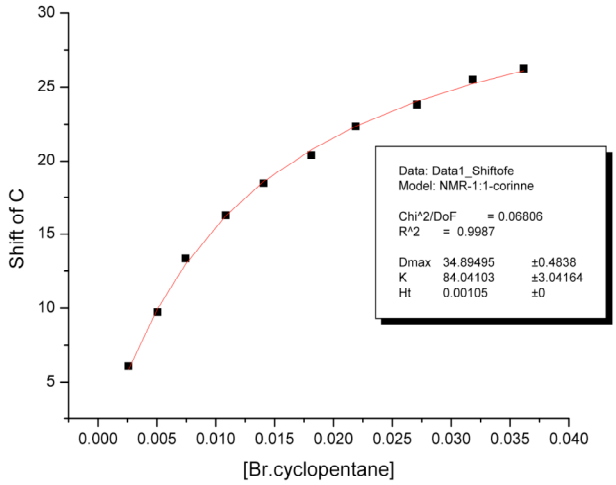

Figure S1. Titration of host **1** with bromocyclopentane

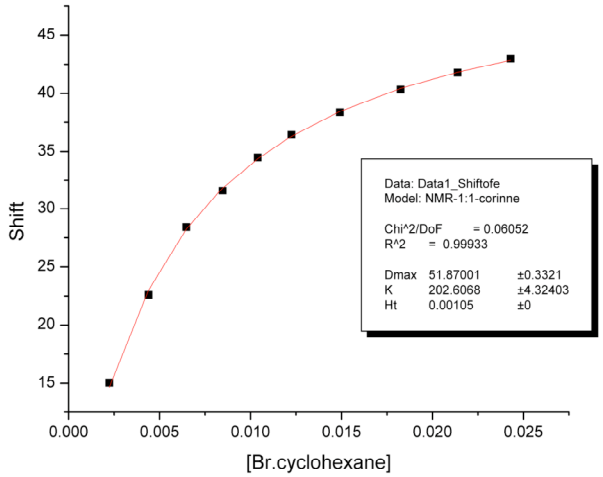

Figure S2. Titration of host **1** with bromocyclohexane

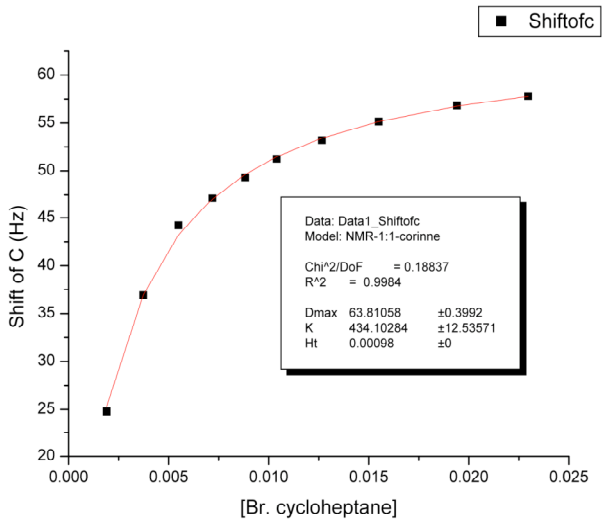

Figure S3. Titration of host **1** with bromocycloheptane

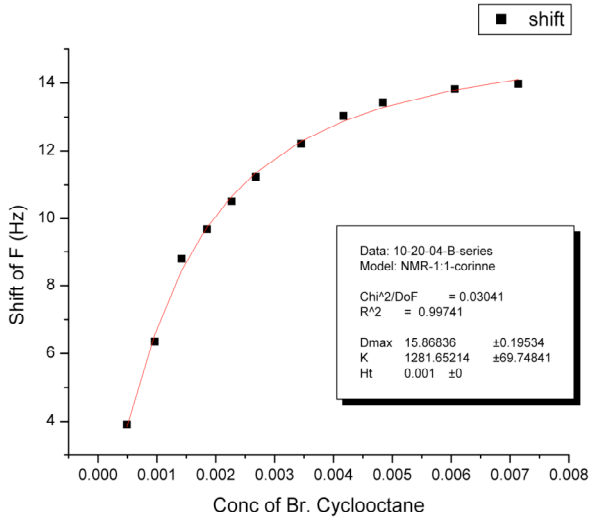

Figure S4. Titration of host **1** with bromocyclooctane

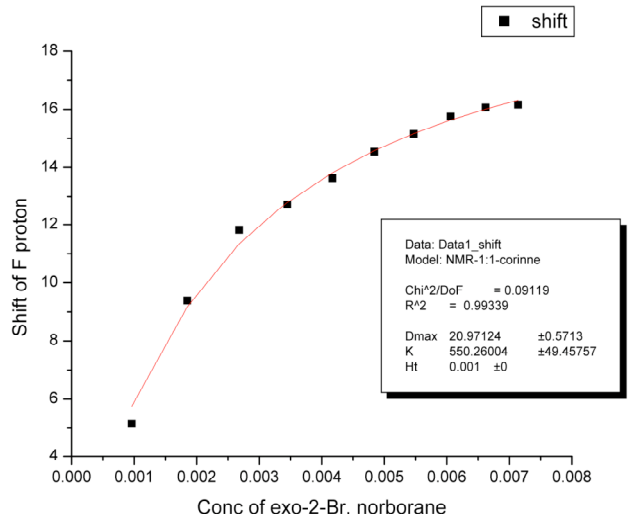

Figure S5. Titration of host **1** with *exo*-2-bromonorborane

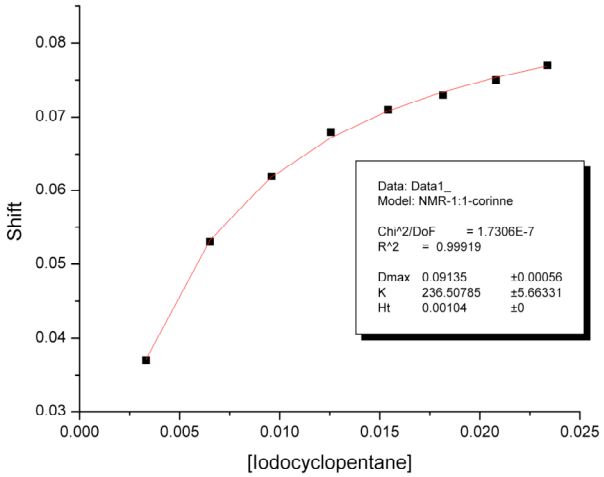

Figure S6. Titration of host **1** with iodocyclopentane

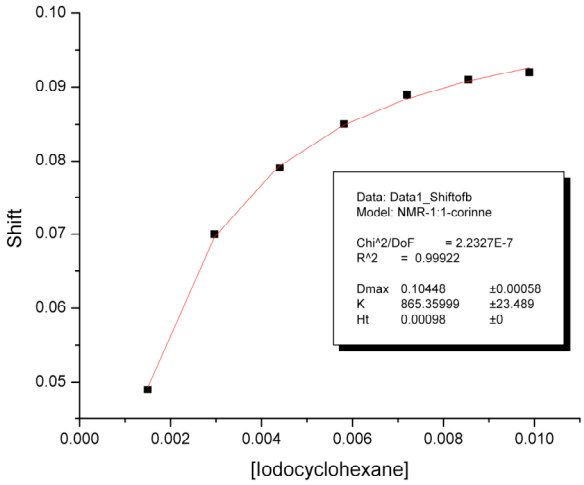

Figure S7. Titration of host **1** with iodocyclohexane

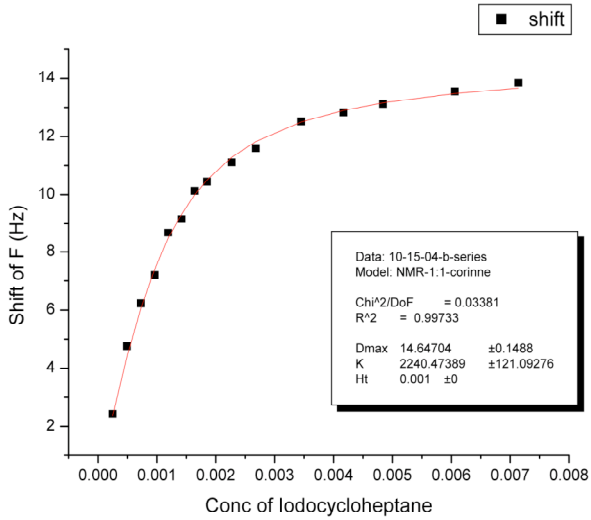

Figure S8. Titration of host **1** with iodocycloheptane

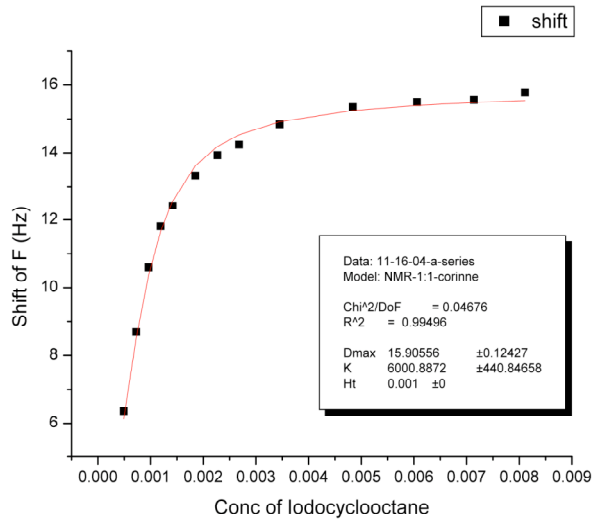

Figure S9. Titration of host **1** with iodocyclooctane

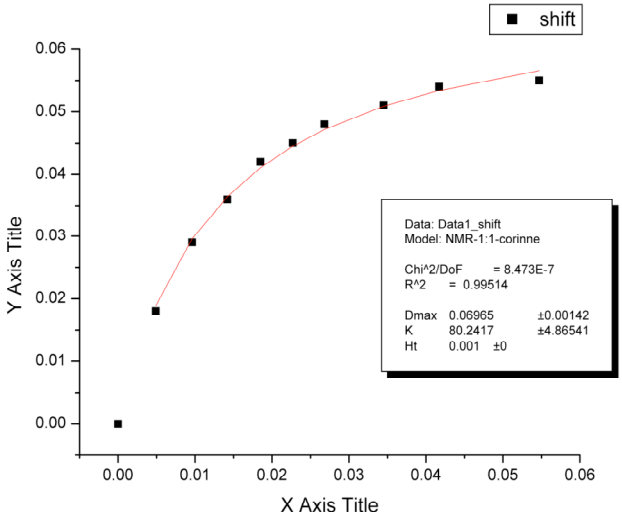

Figure S10. Titration of host **2** with bromocyclopentane

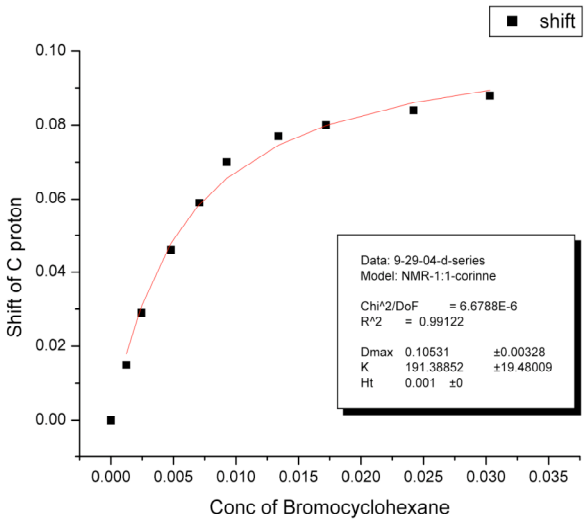

Figure S11. Titration of host **2** with bromocyclohexane

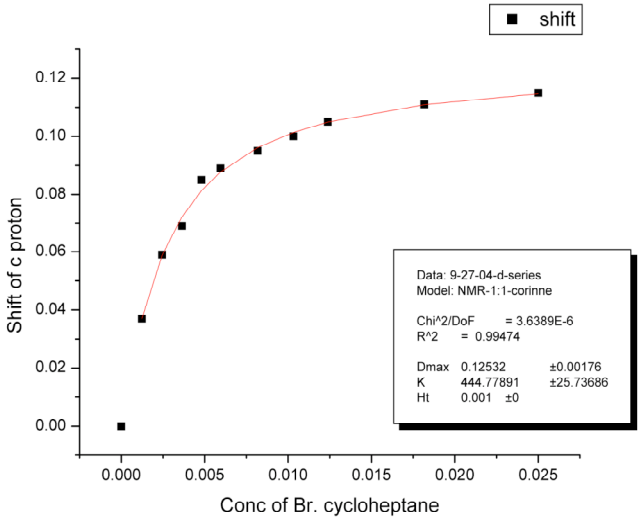

Figure S12. Titration of host **2** with bromocycloheptane

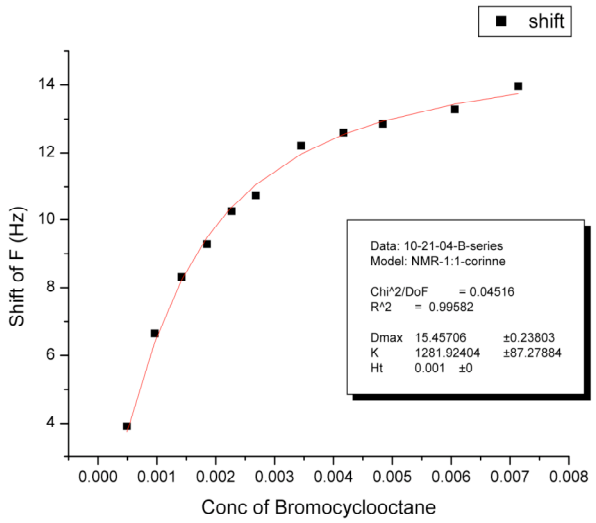

Figure S13. Titration of host **2** with bromocyclooctane

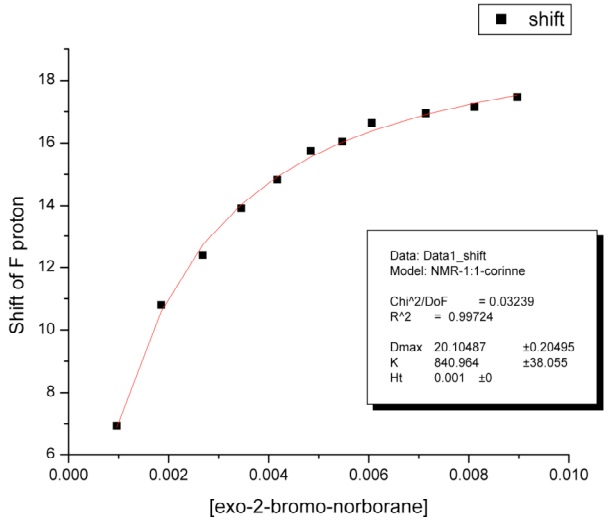

Figure S14. Titration of host **2** with *exo*-2-bromonorborane

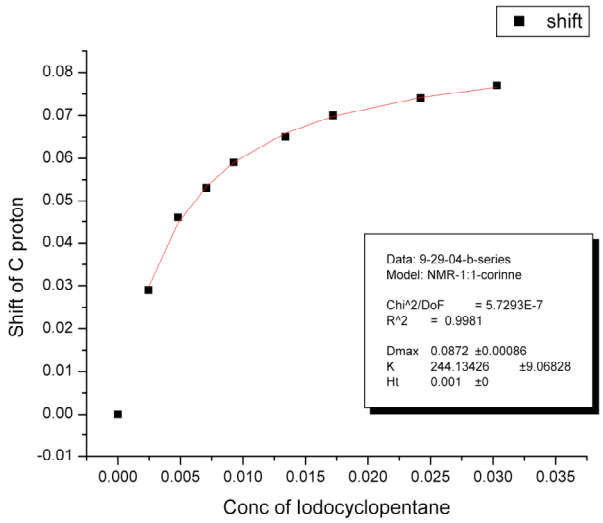

Figure S15. Titration of host **2** with iodocyclopentane

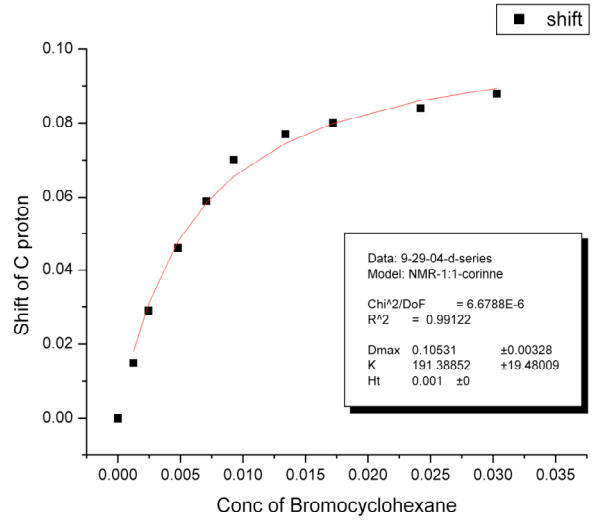

Figure S16. Titration of host **2** with iodocyclohexane

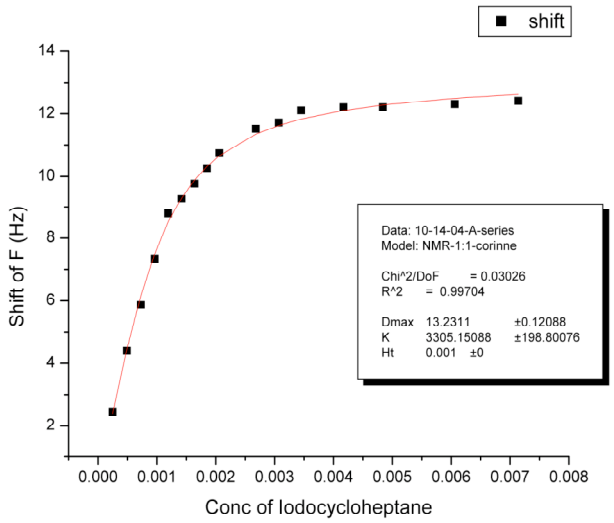

Figure S17. Titration of host **2** with iodocycloheptane

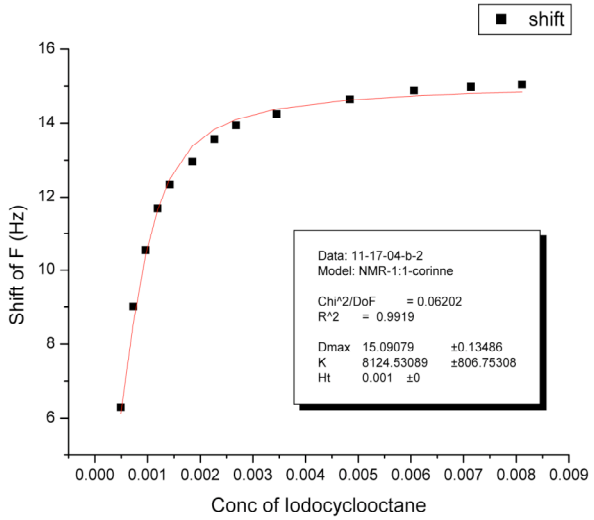

Figure S18. Titration of host **2** with iodocyclooctane