This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Variation of guest selectivity within [Fe₄L₄]⁸⁺ tetrahedral cages through subtle modification of the face-capping ligand.

Alan Ferguson[a]*, Robert W. Staniland[a], Christopher M. Fitchett[a], Marie A. Squire[a], Bryce E. Williamson[a], and Paul E. Kruger[a,b]*

We report here the host-guest behaviour of two isoelectronic [Fe₄L₄]⁸⁺ tetrahedral cages that differ only in the nature of their
10 face-capping ligand and possess either triazine (L1) or benzene (L2) cores. Crystallography reveals these hosts to be flexible and adaptable, while NMR spectroscopy shows them to be selective and discriminating in their host-guest behaviour.

The synthesis of molecular cages has produced an impressive
15 variety of species, many of which are capable of selectively binding guest molecules within their cavities.[1] Selectivity is based upon an interplay between host and guest to achieve the best complementarity between size, shape, bonding and electronic factors with the 'best fit' yielding highest stability.
20 The high affinity for specific guests displayed by these cages bodes well for their use in separations,[2] ion binding,[3] drug delivery[4] and catalysis.[5] Importantly, the host-guest chemistry of these nano-capsules can be modified through change of the organic components or by external perturbation. For example,
25 the incorporation of large ancillary groups on the cage forming ligands has been shown to compress the cavity volume and alter the selectivity and motion of the encapsulated guests.[6] Likewise, it is possible to regulate guest exchange kinetics by capping the apertures through which
30 guest ingress/egress occurs.[7] Further, it has been shown that light can be used to reversibly control encapsulation processes whereby photo-isomerisation of a guest causes it to be ejected from the host because of shape incompatibility.[8] Moreover, the use of electron-poor ligands in the synthesis of cages has
35 rendered them capable of binding organic molecules in aqueous media and to accelerate Diels-Alder reactions.[9]

We recently reported the first tetrahedral cage to show spin crossover (SCO) behaviour, [Fe₄L₄](BF₄)₈, where **L** is the face-capping ligand derived from the sub-component self-
40 assembly of 2,4,6-tris(4-aminophenoxy)triazine and 2-imidaz-olecarboxaldehyde, along with preliminary ¹⁹F NMR data tracking the ingress/egress of the BF₄⁻ guest.[10] Naturally, the switchable paramagnetic nature of this cage impinged upon its host-guest behaviour. To more fully delineate the influences
45 that SCO behaviour has upon guest exchange a thorough study of the host-guest behaviour of related diamagnetic cages is required. We report here the synthesis, structural characterisation and varied host-guest behaviour of two cages featuring iso-electronic ligands with either electron-poor
50 triazine-ring (**L1**) or electron-rich benzene-ring (**L2**) cores (Scheme 1).

The self-assembly of 2,4,6-tris(4-aminophenoxy)triazine, 2-
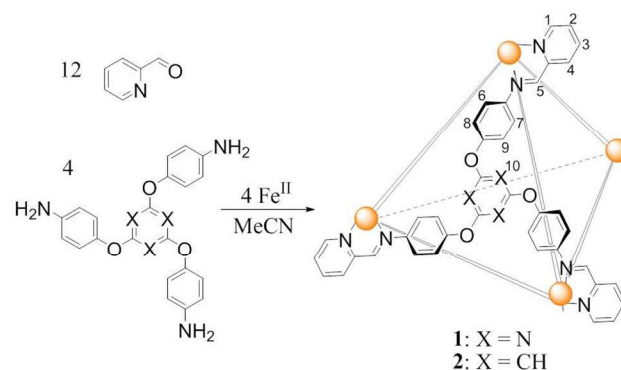
Scheme 1 Sub-component self-assembly of tetrahedral cages from 2,4,6-tris(4-aminophenoxy)triazine or 1,3,5-tris(4-aminophenoxy)benzene, 2-
55 pyridinecarboxaldehyde and Fe(II) in acetonitrile to yield the corresponding face-capped tetrahedra, [Fe₄L₄]⁸⁺.

pyridinecarboxaldehyde and either Fe(BF₄)₂, Fe(OTf)₂, Fe(PF₆)₂ or Fe(ClO₄)₂ in MeCN solution in 4:4:12 stoichiometry yields [Fe₄L1₄]⁸⁺ cages, **1** (Scheme 1). Vapour
60 diffusion of diisopropyl ether into the reaction mixtures containing either Fe(BF₄)₂ or Fe(OTf)₂ produced deep purple crystals suitable for single-crystal X-ray diffraction studies.†

The structure of [BF₄⊂**1**](BF₄)₇ was refined in the triclinic space group *P*–1 (ESI), while [OTf⊂**1**](OTf)₇ was refined in
65 the monoclinic *C*2/*c* space group (Fig. 1, ESI). The encapsulated BF₄⁻ anion shows strong F···π interactions (average F···centre-of-ring distance of 3.04 Å),[11] while the encapsulated OTf⁻ anion is disordered over three positions. Each of the three orientations shows CF₃···π interactions at an
70 average distance of 3.05 Å, which again suggests strong interaction despite the positional disorder. The average Fe···Fe distance within [BF₄⊂**1**](BF₄)₇ and [OTf⊂**1**](OTf)₇ tetrahedra is 14.05 and 14.23 Å, whilst the accessible volumes of their cavities are 105 and 119 Å³, respectively.[12] Clearly the
75 flexible nature of the face-capping ligand allows the tetra-hedron to adapt to better match the guest encapsulated within the cavity. The expansion of the cage within [OTf⊂**1**](OTf)₇ allows the larger OTf⁻ anion to be encapsulated, although it is with a squeeze, as it occupies ~72% of the available volume,
80 which is larger than that occupied by BF₄⁻ in [BF₄⊂**1**](BF₄)₇ (~51%), and lies outside that anticipated for optimal guest encapsulation (55 ± 9%).[13] Both complexes pack together via face-to-face π-π interaction between two neighbouring triazine rings to give a dimeric unit (ESI).
85 The formation of BF₄⁻, OTf⁻, PF₆⁻ and ClO₄⁻ derivatives of the **L1**-based cage was also confirmed by NMR spectroscopy
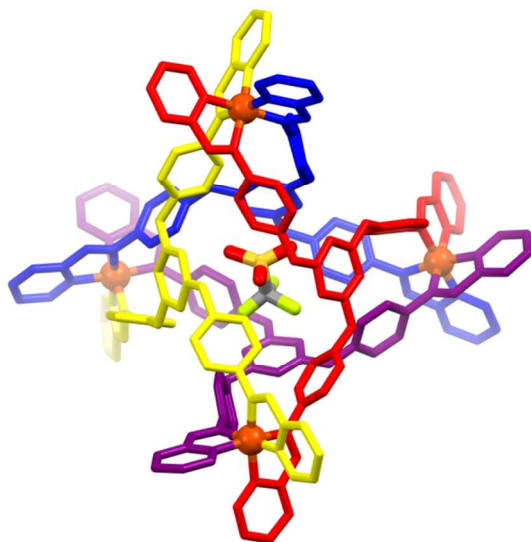
Fig. 1 Crystal structure of [OTf⊂**1**](OTf)$_7$, showing one orientation of the encapsulated OTf⁻ anion. All hydrogen atoms, solvent molecules and lattice anions have been removed for clarity.

and mass spectrometry.† Each ¹H NMR spectrum shows a
5 single set of peaks consistent with *T* point symmetry, while mass spectrometry confirms the presence of the [Fe$_4$**L1**$_4$]$^{n+}$ species. ¹⁹F NMR spectroscopy reveals resonances for both 'free' and encapsulated ions in ~7:1 ratio for BF$_4^-$, OTf⁻ and PF$_6^-$. While the encapsulation of ClO$_4^-$ is indicated by ¹H
10 NMR spectroscopy and mass spectrometry data, it was definitively proven by the experiments reported below.

To assess the host-guest behaviour more fully we attempted to synthesise an empty cage using Fe(NTf$_2$)$_2$ featuring the larger triflimide anion but were unsuccessful. Several species
15 were observed in the ¹H NMR spectrum, suggesting an important role for the smaller anions in templating the formation of this cage. Nonetheless, we devised a cycle of competition experiments to determine the relative binding affinities of anions across a range of potential guests.
20 Beginning with [BF$_4$⊂**1**](BF$_4$)$_7$ we added an equivalent of other potential anionic guests and tracked any changes in both the cage and anions by ¹H and ¹⁹F NMR spectroscopy. Interestingly, we found that when a CD$_3$CN solution containing [BF$_4$⊂**1**](BF$_4$)$_7$ was treated with an alternate anion
25 (PF$_6^-$, ClO$_4^-$ or OTf⁻) at room temperature there was no exchange of BF$_4^-$ for these 'competing' anions over several days. However, if the solutions were heated at 50 °C then exchange of the BF$_4^-$ guest occurred over a period of 12-18 hours for these competing anions. Both PF$_6^-$ and ClO$_4^-$
30 completely displaced the BF$_4^-$ anion as evidenced by the disappearance of the peak at δ −160.6 (due to bound BF$_4^-$), and the appearance of a doublet peak corresponding to encapsulated PF$_6^-$ at δ −73.3 and −75.2. OTf⁻ displaced the BF$_4^-$ anion as demonstrated by the appearance of a new peak
35 at δ −77.7, however, the two anions remain in equilibrium, as evidenced by the retention of a peak at δ −160.6 in the ¹⁹F NMR spectrum, even after prolonged heating.

A series of competitive binding experiments were also conducted whereby all possible combinations of Fe(X)$_2$ salts
40 (X = PF$_6^-$; OTf⁻; ClO$_4^-$; BF$_4^-$) in 2:2 stoichiometry were

reacted with the ligand sub-components (ESI). As anticipated, only PF$_6^-$ was bound within the cavity when Fe(BF$_4$)$_2$ was used in combination with Fe(PF$_6$)$_2$. In the case of Fe(BF$_4$)$_2$ *vs.* Fe(OTf)$_2$, the cage selectively formed around the OTf⁻ ion
45 despite the earlier exchange experiment suggesting that a mixture of [BF$_4$⊂**1**]$^{7+}$ and [OTf⊂**1**]$^{7+}$ might be observed. These experiments allowed the following binding preference for cage **1** to be determined: PF$_6^-$ > OTf⁻ > ClO$_4^-$ > BF$_4^-$. Having established that BF$_4^-$ was the most weakly bound
50 anion, we then introduced some solvent species (benzene, CHCl$_3$, CCl$_4$) to CD$_3$CN solutions of [BF$_4$⊂**1**](BF$_4$)$_7$ to determine if they too could displace BF$_4^-$. However, none of these potential guests displaced BF$_4^-$, which is not too surprising given the highly cationic nature of the cage and the
55 fact that the cage walls within **1** are replete with electron-poor triazine-rings that interact strongly with anionic species.[14]

We next used electron-rich 1,3,5-tris(4-aminophenoxy)-benzene in combination with 2-pyridinecarboxaldehyde in the sub-component self-assembly reaction with Fe(II) salts to
60 yield a series of [Fe$_4$**L2**$_4$]$^{8+}$ cages, **2**, (Scheme 1). The face-capping ligand **L2** is iso-electronic with, and possesses near identical metric parameters to, **L1.** Any variation in binding affinity of the cages could then be attributed to differences in their electron- rich *vs.* poor nature. Vapour diffusion of Et$_2$O
65 into the deep purple reaction mixture resulting from Fe(NTf$_2$)$_2$ produced crystals suitable for single-crystal X-ray diffraction studies. The structure of [**2**](NTf$_2$)$_8$ was refined in the monoclinic space group $P2_1/c$ (ESI). There are two crystallographically distinct cages in the asymmetric unit,
70 with average Fe-Fe separations of 14.29 and 14.40 Å, respectively. These Fe-Fe distances result in an increased cavity volume in **2** relative to **1** of 148 and 150 Å^3.[12] It was not possible to determine the exact nature of the encapsulated guest due to significant disorder, but we suspect solvent
75 molecules reside within the cavity as the NTf$_2^-$ anion is too large to fit. The formation of the BF$_4^-$, OTf⁻, NTf$_2^-$, PF$_6^-$ and ClO$_4^-$ derivatives of the **L2**-based cage has been confirmed by NMR spectroscopy and mass spectrometry. Each ¹H NMR spectrum shows one set of peaks consistent with *T* point
80 symmetry, while mass spectrometry confirms the presence of [Fe$_4$**L2**$_4$]$^{n+}$ species. ¹⁹F NMR spectroscopy reveals that OTf⁻ and PF$_6^-$ are bound within the cavity however; NTf$_2^-$ and BF$_4^-$ are not (or are in rapid exchange) due to the presence of only one peak within their spectra consistent with 'free' anion.

85 Comparison of the ¹H NMR spectra of **2** in its 'guest-free' or 'guest-bound' forms reveals interesting differences in many proton resonances but most significantly in the peaks for the phenyl protons H^6, H^7, H^8, H^9 and H^{10} from the three ligand arms and the central benzene ring (Fig. 2 and Scheme 1). In
90 its 'guest-free' form (BF$_4^-$, NTf$_2^-$ and ClO$_4^-$) these peaks are noticeably broadened due to fluxional/rotational behaviour of the phenyl rings. However, in their 'guest-bound' form (OTf⁻ and PF$_6^-$) these peaks sharpen, resolve cleanly to doublets and either shift upfield (H^6, H^{10}) or down-field (H^7, H^8, H^9),
95 suggesting the guests 'lock-down' the ligand arms to inhibit their dynamic behaviour (Fig. 2).

To better determine the host-guest behaviour of **2** a series of titrations were conducted whereby potential guests were
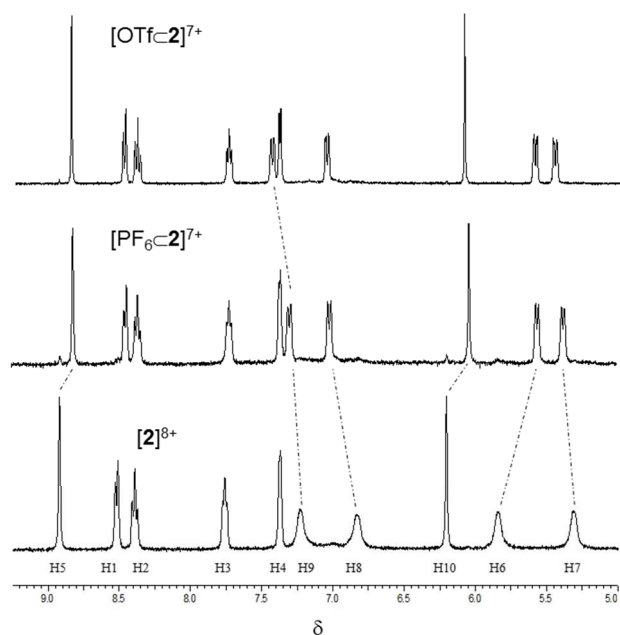
Fig. 2 Partial ^{1}H NMR spectra for the titration of 'guest-free' cage [**2**]$^{8+}$ (bottom) with PF$_6^-$ to give [PF$_6$⊂**2**]$^{7+}$ (middle) and then subsequently with OTf$^-$ to give [OTf⊂**2**]$^{7+}$ (top). (CD$_3$CN, 400 MHz, 298 K).

added to 'guest-free' **2** in small increments and the host-guest formation was monitored through ^{1}H NMR spectroscopy (Fig. 2 and ESI). Complete conversion to 'guest-bound' **2** occurred when OTf$^-$ or PF$_6^-$ were added (ESI), however, incomplete conversion resulted when excess benzene was added (ESI). No other guest trialled (BF$_4^-$, ClO$_4^-$, NTf$_2^-$, CHCl$_3$, CCl$_4$) was observed to bind. From these data binding constants for OTf$^-$ and PF$_6^-$ were determined as $9.9(\pm1.0) \times 10^4$ M^{-1} and $2.61(\pm0.16) \times 10^4$ M^{-1}, respectively.[15] The binding constant for benzene could not be determined due to overlap of peaks derived from **2** and [benzene⊂**2**]$^{8+}$, however, from the ^{1}H NMR spectrum we estimate 1:1 stoichiometry.

A sequential guest exchange experiment was then performed and tracked through ^{1}H and ^{19}F NMR spectroscopy by firstly titrating PF$_6^-$ against 'guest-free' **2** to yield [PF$_6$⊂**2**]$^{7+}$, thereafter OTf$^-$ was titrated against the newly formed [PF$_6$⊂**2**]$^{7+}$ species to give [OTf⊂**2**]$^{7+}$ (Fig. 2). From these experiments the order of guest binding preference for cage **2** was then determined as: OTf$^-$ > PF$_6^-$ > benzene >>> BF$_4^-$, ClO$_4^-$, NTf$_2^-$, CHCl$_3$, CCl$_4$.

In conclusion, it is clear that dramatic change in guest binding preference can be affected by subtle electronic change in the face-capping ligands in [Fe$_4$L$_4$]$^{8+}$ tetrahedral cages. The electron-poor triazine-based cage **1** has higher affinity for large anionic guests (that fit within its void) over small ones, although it will bind both with accommodating fashion. In contrast, however, cage **2** built from electron-rich face-capping ligands binds larger anions only and not small anions. Notably, it also binds benzene, a neutral guest, but of comparable size to OTf$^-$ and PF$_6^-$. Clearly a subtle interplay between guest size, charge and the electronic nature of the host is operative and determines whether guest inclusion occurs. We are currently extending this study to include other face-capping ligands of varied electronic nature to screen additional anionic and neutral guest preferences with the view to include related SCO cages to study the interplay between host-guest and SCO behaviour. We will report results from these studies in due course.

Notes and references

^{a}Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand.
^{b}MacDiarmid Institute for Advanced Materials and Nanotechnology, Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand. E-mail: paul.kruger@canterbury.ac.nz

1 H. Amouri, C. Desmarets, J. Moussa, *Chem. Rev.*, 2012, **112**, 2015; M.M.J. Smulders, I.A. Riddell, C. Browne, J.R. Nitschke, *Chem. Soc. Rev.*, 2013, **42**, 1728; M.D. Ward, *Chem. Commun.* 2009, 4487.
2 E. Huerta, G. A. Metselaar, A. Fragoso, E. Santos, C. Bo, J. de Mendoza, *Angew. Chem. Int. Ed.*, 2007, **46**, 202; W. Meng, B. Breiner, K. Rissanen, J.D. Thoburn, J.K. Clegg, J.R. Nitschke, *Angew. Chem. Int. Ed.*, 2011, **50**, 3479.
3 R. Custelcean, *Chem. Commun.*, 2013, **49**, 2173; S. Goetz, P.E. Kruger, *Dalton Trans.*, 2006, 1277; D.A. McMorran, P.J. Steel, *Angew. Chem. Int. Ed.*, 1998, **37**, 3295.
4 J.E.M. Lewis, E.L. Gavey, S.A. Cameron, J.D. Crowley, *Chem. Sci.* 2012, **3**, 778; Z. Ma, B. Moulton, *Coord. Chem. Rev.* 2011, **255**, 1623; N.P. E. Barry, O. Zava, P.J. Dyson, B. Therrien, *Chem. Eur. J.* 2011, **17**, 9669.
5 M. Yoshizawa, J.K. Klosterman, M. Fujita, *Angew. Chem. Int. Ed.*, 2009, **48**, 3418; J.S. Mugridge, R.G. Bergman and K.N. Raymond, *J. Am. Chem. Soc.*, 2012, **134**, 2057.
6 Y. Fang, T. Murase, S. Sato and M. Fujita, *J. Am. Chem. Soc.*, 2013, **135**, 613.
7 S. Zarra, M.M.J. Smulders, Q. Lefebvre, J.K. Clegg and J.R. Nitschke, *Angew. Chem. Int. Ed.*, 2012, **51**, 6882.
8 H. Dube, D. Ajami and J. Rebek, Jr., *Angew. Chem. Int. Ed.*, 2010, **49**, 3192; H. Dube and J. Rebek, Jr., *Angew. Chem. Int. Ed.*, 2012, **51**, 3207.
9 M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi and K. Ogura, *Nature*, 1995, **378**, 469; Y. Inokuma, G.H. Ning and M. Fujita, *Angew. Chem. Int. Ed.*, 2012, **51**, 2379; M. Yoshizawa, M. Tamura, M. Fujita, *Science*, 2006, **312**, 251
10 A. Ferguson, M.A. Squire, D. Siretanu, D. Mitcov, C. Mathonière, R. Clérac and P.E. Kruger, *Chem. Commun.*, 2013, **49**, 1597.
11 A. Frontera, *Coord. Chem. Rev.*, 2013, **257**, 1716.
12 PLATON VOIDS probe diameter 1.2 Å, grid 0.2 Å, A. L. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7.
13 S. Mecozzi and J. Rebek, Jr., *Chem. Eur. J.*, 1998, **4**, 1016.
14 B.L. Schottel, H.T. Chifotides, K.R. Dunbar, *Chem. Soc. Rev.*, 2008, **37**, 68.
15 Y.R. Hristova, M.M.J. Smulders, J.K. Clegg, B. Breiner and J.R. Nitschke, *Chem. Sci.*, 2011, **2**, 638.