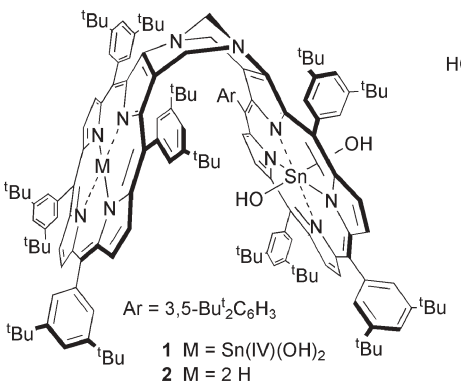
Cavity effect amplification in the recognition of dicarboxylic acids by initial ditopic H-bond formation followed by kinetic trapping†

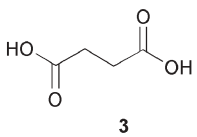
Peter R. Brotherhood, Richard A.-S. Wu, Peter Turner and Maxwell J. Crossley*

Received (in Cambridge, UK) 6th October 2006, Accepted 10th November 2006
First published as an Advance Article on the web 29th November 2006
DOI: 10.1039/b614575b

Di[dihydroxotin(IV)] Tröger's base bis-porphyrin 1, a host molecule with two internal and two external guest interaction sites, binds ⩽ 1 equivalent of dicarboxylic acid quantitatively within the chiral cavity, a regioselectivity amplified by initial ditopic H-bond formation, followed by kinetic trapping.

Dihydroxotin(IV) porphyrins have been used extensively as building blocks in the formation of supramolecular complexes[1] and in molecular recognition.[2] Ligand exchange with protic oxygen molecules occurs at these systems to form strong six-coordinate O-bound complexes, with the elimination of water, that are readily studied by NMR.[3] It is proposed that the first step in the ligand exchange process is a H-bond equilibrium complex between the *in situ* hydroxo ligand and the incoming guest ligand.[4] Observations in the current study can only be rationalised by such a process. A mechanism of this nature offers the possibility for guests to organise to a thermodynamic interaction with the host prior to formation of the ester-like RO–Sn bond. There is scope for application of this binding phenomenon to the formation of intricate self-assembled complexes with stability constants far in excess of those available through the use of more labile assembly interactions. Herein we report a strategy that combines dihydroxotin(IV) porphyrin carboxylate binding chemistry with rigid cavity host morphology and elucidate a mechanism that leads to the quantitative, ditopic, internal cavity binding of dicarboxylic acids.





Host **1**[5] possesses a relatively rigid chiral cleft and the orientation of the internal metal binding sites makes it appropriate for the ditopic association of bridging guest ligands in the interior of the cavity.[6] The cavity also possesses two external binding sites that are more sterically accessible. X-ray crystal structure analysis of host **1** (Fig. 1*a*,*b*)‡ confirms these design features. Products of ligand exchange at host **1** can be identified and characterised by NMR. Summation of the porphyrin ring current effects results in significant shifts for internally bound ligands which resonate 1.5 to 3.5 ppm upfield of those bound at the exterior.

Regioselective binding of dicarboxylic acids ditopically at the interior of the cavity extends to malonic acid, succinic acid **3**, glutaric acid and adipic acid. When introduced to host **1** at ⩽ 1 mole equivalent,[7] each of these dicarboxylic acids binds monotopically within the cavity in under 10 min and subsequently no free dicarboxylic acid is detected. Times for complete ditopic

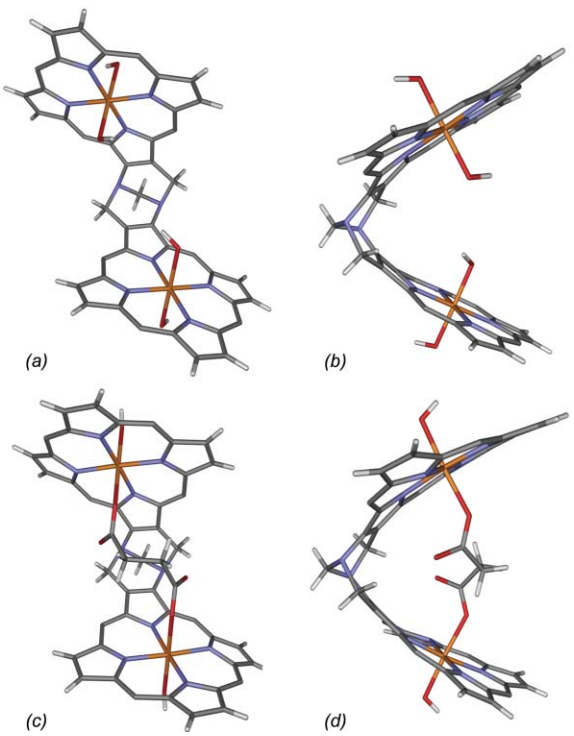


Fig. 1 X-ray crystal structures. Eight *meso*-3,5-Bu$^t_2$C$_6$H$_3$ groups removed for clarity. *(a)* Host **1** view into cavity, *(b)* side-on view. *(c)* Host **1**·succinate complex **6** view into cavity, 70% occupancy succinate shown, *(d)* side-on view. Complex **6** resides on a 2-fold axis passing through the centre of the succinate ligand and the bis-porphyrin bridgehead.

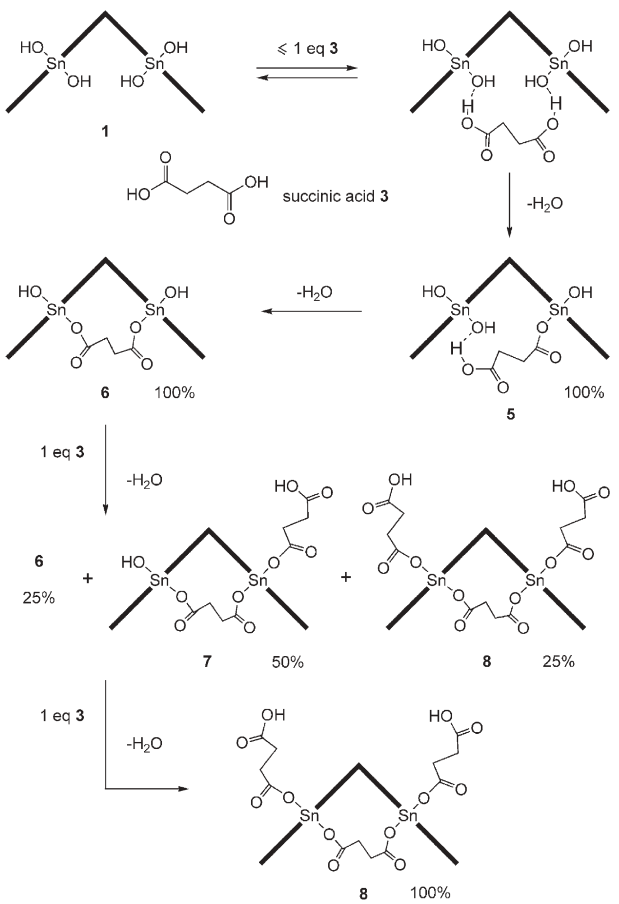
School of Chemistry, The University of Sydney, NSW 2006, Australia. E-mail: m.crossley@chem.usyd.edu.au; Fax: +61 2 9351 3329; Tel: +61 2 9351 2751

† Electronic supplementary information (ESI) available: Synthetic details, ^{1}H NMR titration spectra and X-ray crystallographic data. See DOI: 10.1039/b614575b

binding, however, increase markedly with the length of the dicarboxylic acid from < 2 min for malonic acid, 15 min for succinic acid **3**, 30 min for glutaric acid, to 30 h for adipic acid. The X-ray crystal structure of one of these products, host **1**·succinate **6** is given in Fig. 1.

Of particular interest in the crystal structure of complex **6** is the orientation of the succinate ligand when bound in the cavity. Succinate is bound in two conformations in a 70 : 30 ratio. The 70% occupancy is shown in Fig. 1*c*,*d*. This conformation shows gauche interactions and projection of the succinate carbonyl oxygens into the rear of the cavity. The 30% occupancy succinate adopts antiperiplanar geometry and the carbonyl oxygens project to the mouth of the cavity, leaving what appears as void space at the interior. Apparently favourable interaction between the carbonyl oxygen and the interior of the cavity is sufficient to counter the energy penalty due to eclipsing interactions in the guest. Structural changes are also evident in the host molecule on binding of succinic acid **3**. The porphyrin macrocycles in complex **6** are distorted from planarity compared with those of the host **1** and the Sn…Sn distance is reduced from 8.60 Å to 8.48 Å.

Examination by ^{1}H NMR of the binding to host **1** of succinic acid **3** provides a basis for understanding the origins of the high regioselectivity seen in the binding of this series of dicarboxylic acids. The mechanism of succinate binding to host **1** is summarised in Scheme 1. Addition of ⩽ 1 equivalent of succinic acid **3** to host **1**[7] results in interaction first at the interior of the cavity in the form of a ditopic H-bonded complex. Protonation of one hydroxo ligand, its dissociation as water, and condensation of the carboxylate anion with the tin(IV) centre occurs rapidly to yield the monotopically bound complex **5** (Fig. 2*b*, inset). The ditopic H-bond complex precursor is not detected by ^{1}H NMR. Pre-organisation of the dicarboxylic acid in the cavity renders the first ligand exchange process effectively intramolecular, resulting in rate enhancement. Ligand exchange rates for monodentate acids at monomeric tin(IV) porphyrin systems can be much slower, allowing observation of the initial H-bonded complex.[4] Ligand exchange at the second internal tin(IV) binding site then occurs to afford the ditopic complex **6** in under 15 min (Fig. 2*c*,*d*). Although two distinct conformations of bound succinate are seen in the solid state structure, the sharp resonances for bound succinate (Fig. 2) indicate fast conformational changes on the NMR timescale and therefore that interconversion of these binding modes does not require Sn–O bond breakage. When internal cavity binding is complete exchange of external hydroxo ligands commences. At ⩽ 2.0 equivalents of succinic acid **3** a mixture of the 1 : 1



Scheme 1 Mechanism of succinic acid **3** binding to host **1**, representative of binding mechanism for malonic, glutaric and adipic acids. Porphyrin macrocycles and methanodiazocine bridge represented by the bold lines.

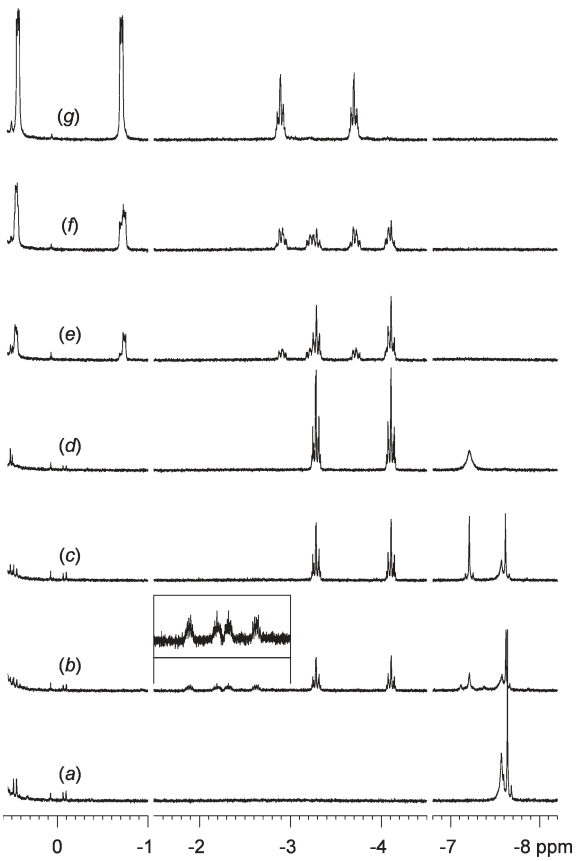


Fig. 2 ^{1}H NMR (400 MHz, $CDCl_3$) spectra showing the titration of succinic acid **3** with host **1**.[7] 0.7 to −1.0 ppm, external succinate ligands, −1.5 to −4.5 ppm, internal succinate ligands, −6.8 to −8.2 ppm, hydroxo ligands. *(a)* Host **1**, *(b)* host **1** + 0.5 equiv. **3**, 3 min. Inset shows expansion of signals for **3** bound monotopically inside the cavity, complex **5**. *(c)* Host **1** + 0.5 equiv. **3**, 15 min. Complete internal ditopic binding, complex **6** and residual **1**. *(d)* + 0.5 equiv. **3**, 1.0 equiv. total, 15 min, complex **6**. *(e)* + 0.5 equiv. **3**, 1.5 equiv. total, 10 min, predominantly complexes **6** and **7**. *(f)* + 0.5 equiv. **3**, 2.0 equiv. total, 10 min, complexes **6**, **7** and **8**. *(g)* + 1.0 equiv. **3**, 3.0 equiv. total, 10 min, complex **8**.

complex **6**, the 2 : 1 complex **7** and the 3 : 1 complex **8** is formed (Fig. 2*e*,*f*). Addition of a third equivalent results in ligand exchange at the remaining external binding sites and quantitative formation of the 3 : 1 complex **8** (Fig. 2*g*). Hydroxo ligand resonances are included in Fig. 2 and changes in these are easily rationalised by the proposed binding mechanism. At the completion of ditopic binding at the interior of the cavity (Fig. 2*d*) the resonance for the exterior hydroxo ligands becomes broadened by exchange with water expelled from the cavity during the binding process. Satellites to the central ^{119}Sn(IV) and ^{117}Sn(IV) nuclei are clear (host **2** −7.65 ppm (2 H, s, satellites $^{2}J_{\mathrm{Sn-H}}$ 35 Hz), complex **6** −7.21 ppm (2 H, s, satellites $^{2}J_{\mathrm{Sn-H}}$ 34 Hz)).

The chirality of host **1** delivers additional information about binding modes. When subjected to the chiral environment of the cavity the diastereotopicity of the succinate methylene protons is evident in the complex splitting of their NMR resonances. External succinate ligands are also bound in a chiral environment, however, with less constraint on their conformation, and as a result the signals for diastereotopic protons on these groups average to α- and β-methylene. The asymmetric environment of the cavity is especially evident when the C_2 symmetry of the complex is broken, as in the monotopically bound succinic acid complex **5** (inset, Fig. 2*b*) and in the 2 : 1 complex **7**. In these instances each of the four succinate methylene protons gives rise to a multiplet reflecting the complexity of their spin system. These signals for the 2 : 1 complex **7** are almost coincident with those for the 1 : 1 complex **6** and the 3 : 1 complex **8** (Fig. 2*e*,*f*). The obvious diastereotopicity of the methylene protons for the first equivalent of bound succinate confirms the chemical shift data, that initial binding is in the interior of the cavity.

Control experiments were performed to determine the detail of the mechanism that leads to the quantitative internal cavity binding exhibited by succinic acid **3** to host **1**. (see ESI†) Acetic acid **4** was bound to di[dihydroxotin(IV)] host **1** to determine the importance of the second H-bond donor site on the succinate guest, and acetic acid **4** and succinic acid **3** were bound to dihydroxotin(IV)-free-base host **2** to determine the importance of the second internal H-bond acceptor site in the interior of the cavity. Both these features of the host–guest system were identified as essential to quantitative internal cavity binding. Acetic acid **4** (1 equivalent) binds to host **1** with only a 1.5-fold preference for internal cavity positions at 3 min, the time required for quantitative association of succinic acid **3** in the interior of the cavity. Equilibration occurs over 100 min to give a 4.5 : 1 ratio of acetates bound at the interior. Dihydroxotin(IV)-free-base host **2** binds the first equivalent of acetic acid **4** or succinic acid **3** predominantly at the exterior of the cavity, with only trace ligand substitution at the internal position and trace formation of the dicarboxylatotin(IV)-free-base complex. This indicates that contributors to the above cavity effect such as desolvation of guest and cavity are unimportant compared to the facility to form H-bonding interactions. For host **2** the free-base porphyrin macrocycle appears simply to pose a steric barrier to H-bond complexation in the interior of its cavity, resulting in ligand exchange at the exterior.

From these studies, a mechanism that accounts for the high selectivity of binding of dicarboxylic acids in host **1** emerges. A pre-equilibrium H-bond step in this binding process results in the formation of a thermodynamic product in the interaction of the dicarboxylic acid guest and the host, a ditopic H-bond complex in the interior of the cavity. This complex is subsequently removed from pre-equilibrium by formation of one ester-like tin(IV)–carboxylate bond and the dissociation of a molecule of water,[4] thereby syphoning material towards quantitative *intra*-cavity binding. Formation of the second tin(IV)–carboxylate bond in the cavity is then an intramolecular reaction, the rate of which is determined by the degree of organisation required of both host and guest to facilitate binding. As the degree of conformational freedom of the dicarboxylic acid increases with chain length a greater period of time is required for adoption of a bound conformation.

In ongoing studies we have found that this phenomenon, a labile pre-equilibrium interaction followed by kinetic trapping by tin(IV)–carboxylate bond formation, also leads to amplification of the cavity effect in a zinc(II)-dihydroxotin(IV) Tröger's base bis-porphyrin[5] host system, leading to enantioselective *intra*-cavity binding of α-amino acids. These studies will be reported shortly.

We thank the Australian Research Council for a Discovery Grant to MJC, an Australian Postgraduate Award to RASW and The University of Sydney for an H. B. and F. M. Gritton postgraduate award to PRB.

Notes and references

‡ Crystal structure data for host **1**: model formula $C_{157.50}H_{194}ClN_{11}O_{10.25}Sn_2$, M 2678.07, triclinic, $P\bar{1}$ (#2), a 16.468(9), b 21.274(12), c 23.587(13) Å, α 90.583(9), β 94.483(9), γ 95.907(9)°, V 8193(8) Å^3, D_c 1.086 g cm^{-3}, Z 2, T = 150(2) K, λ(MoKα) 0.71073 Å, μ(MoKα) 0.376 mm^{-1}, N_{ind} 37404 (R_{merge} 0.0656), N_{obs} 29063 ($I > 2\sigma(I)$), $R1(F)$ 0.1848, $wR2(F^2)$ 0.4521. Crystal structure data for complex **6**: model formula $C_{175.20}H_{200.40}N_{10}O_{11.40}Sn_2$, M 2866.04, monoclinic, $C2/c$ (#15), a 31.236(5), b 27.384(7), c 21.366(5) Å, β 115.594(10)°, V 16482(6) Å^3, D_c 1.155 g cm^{-3}, Z 4, T = 123(2) K, λ(synchrotron) 0.56356 Å, μ(synchrotron) 0.199 mm^{-1}, N_{ind} 20278 (R_{merge} 0.0786), N_{obs} 16684 ($I > 2\sigma(I)$), $R1(F)$ 0.0415, $wR2(F^2)$ 0.1177. CCDC 623698–623699. For crystallographic data in CIF format see DOI: 10.1039/b614575b

1 Y. Kim, M. F. Mayer and S. C. Zimmerman, *Angew. Chem., Int. Ed.*, 2003, **42**, 1121; J. E. Redman, N. Feeder, S. J. Teat and J. K. M. Sanders, *Inorg. Chem.*, 2001, **40**, 2486. Review: J. K. M. Sanders, in *The Porphyrin Handbook*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, 1st edn, 2000, vol. 3, p. 347.

2 J. C. Hawley, N. Bampos and J. K. M. Sanders, *Chem.–Eur. J.*, 2003, **9**, 5211; S. J. Webb and J. K. M. Sanders, *Inorg. Chem.*, 2000, **39**, 5920.

3 D. P. Arnold, *Polyhedron*, 1988, **7**, 2225; D. P. Arnold and E. A. Morrison, *Polyhedron*, 1990, **9**, 1331; Y. Tong, D. G. Hamilton, J.-C. Meillon and J. K. M. Sanders, *Org. Lett.*, 1999, **1**, 1343; D. P. Arnold and J. Blok, *Coord. Chem. Rev.*, 2004, **248**, 299.

4 J. C. Hawley, N. Bampos, R. J. Abraham and J. K. M. Sanders, *Chem. Commun.*, 1998, 661.

5 M. J. Crossley, P. Thordarson and R. A.-S. Wu, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2294.

6 M. J. Crossley, L. G. Mackay and A. C. Try, *J. Chem. Soc., Chem. Commun.*, 1995, 1925; M. J. Crossley, T. W. Hambley, L. G. Mackay, A. C. Try and R. Walton, *J. Chem. Soc., Chem. Commun.*, 1995, 1077; P. R. Allen, J. N. H. Reek, A. C. Try and M. J. Crossley, *Tetrahedron: Asymmetry*, 1997, **8**, 1161.

7 Host **1** (3.10 mg, 1.24 μmol) was dissolved in $CDCl_3$ (600 μL) in an NMR tube and dicarboxylic acid solution in d_6-DMSO–$CDCl_3$ (10 : 90, 0.100 M) was added by microlitre syringe in successive 0.5 mole equivalent aliquots to a total of 2.0 equivalents and subsequently a 1.0 mole equivalent aliquot was added to a total of 3.0 mole equivalents. After each addition ^{1}H NMR spectra were recorded at regular intervals until no further spectral changes indicated binding processes were complete. For titration experiments with acetic acid **4**, stock solutions were prepared in d_6-DMSO–$CDCl_3$ (5 : 95, 0.100 M).