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The binding of difunctional neutral guest molecules by novel bis(tripyrrolyl) cryptands†

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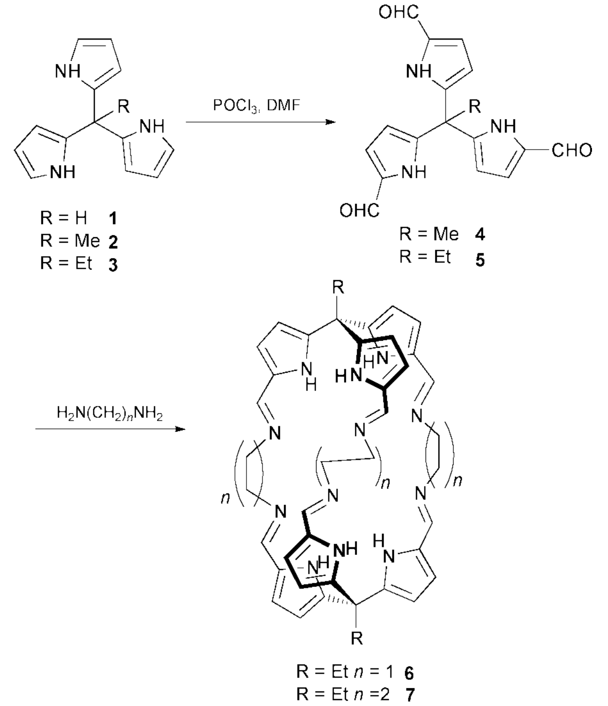
Bis(tripyrrolyl) cryptands are prepared *via* a [2 + 3] Schiff base condensation of formyltripyrrolyls with diamines; an ethyl-spaced hexapyrrole cryptand is shown to bind strongly ethane-1,2-diamine and ethane-1,2-diol in chloroform solution.

Cryptand ligands and carcerand hosts display fascinating coordination and host–guest chemistry due to their ability to wholly encapsulate their guest atoms or molecules.[1,2] Novel and versatile building blocks possessing multiple and convergent donor atoms from which to prepare these cage-like molecular hosts are currently in particular demand. From a practical perspective, the ease with which a building block can be prepared and modified contributes significantly to its degree of future exploitation. Recent developments in calixarene-[3] and more recently porphyrinogen/calixpyrrole-[4] chemistry are prime examples of how simple-to-prepare and robust macrocycles can be skilfully exploited for the coordination of cations[5] and anions.[6]

We were quite surprised therefore that given the recent attention accorded to the chemistry of cyclic, oligomeric pyrrole compounds that the coordination and supramolecular chemistry of tripyrrolylmethane **1** appears to have been sparsely studied.[7] In addition, three-dimensional cryptand-like pyrrole compounds have also remained largely unexplored.[8,9] Herein we report our initial findings on the synthesis of substituted tripyrrolyls and demonstrate the ease with which such molecules can be incorporated into cryptand-like ligands *via* a Schiff base condensation reaction. An ethyl-spaced bis(tripyrrolyl) host **6** is shown to bind strongly ethane-1,2-diamine and ethane-1,2-diol in chloroform solution.

Attempts to formylate tripyrrolylmethane[10] **1** employing a variety of modifications to the Vilsmeier–Haack reaction were unsuccessful. However, adaptation of Bruce's method[11] employing triethyl orthoacetate or triethyl orthopropanoate yielded the methyl and ethyl tripyrrolyls **2** (59%) and **3** (60%) respectively (see Scheme 1). These were easily formylated employing standard Vilsmeier–Haack conditions ($POCl_3$ and DMF) to give the triformylpyrrolyls **4** (84%) and **5** (70%) in good yields. The use of two different triethyl orthoalkanoates demonstrates the generality of this reaction and also illustrates a convenient route to the preparation of further apically-substituted tripyrrolyls.

Treatment of **5** with 1.5 eq. of ethane-1,2-diamine (**en**) or butane-1,4-diamine (**bn**) in THF afforded the cryptand-like Schiff base pyrrole cages **6** and **7**. Recrystallisation from DCM–hexane afforded large, yellow, prismatic crystals of the butyl-spaced cage **7**. Confirmation of the structure was provided by X-ray crystallography‡ (Fig. 1) and also showed the fortuitous inclusion of a molecule of butane-1,4-diamine (**bn**) within **7**. The diaminobutane guest is encapsulated within the cavity *via* 7 hydrogen bonds between the two nitrogen atoms in the guest and 7 different nitrogen atoms in the host. Each nitrogen head of the **bn** molecule is held in place by host hydrogen-bonding



Scheme 1

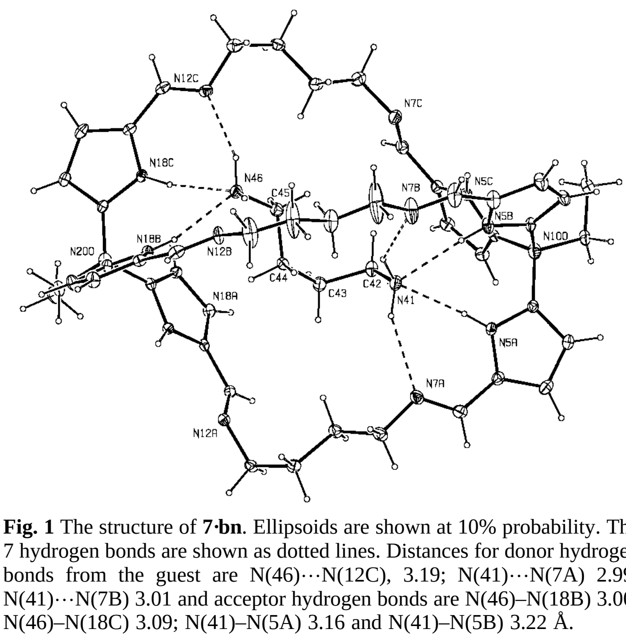


Fig. 1 The structure of **7·bn**. Ellipsoids are shown at 10% probability. The 7 hydrogen bonds are shown as dotted lines. Distances for donor hydrogen bonds from the guest are N(46)···N(12C), 3.19; N(41)···N(7A) 2.99; N(41)···N(7B) 3.01 and acceptor hydrogen bonds are N(46)–N(18B) 3.00; N(46)–N(18C) 3.09; N(41)–N(5A) 3.16 and N(41)–N(5B) 3.22 Å.

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† Electronic supplementary information (ESI) available: experimental procedures, spectroscopic data and titration protocol. See http://www.rsc.org/suppdata/cc/b1/b104077b/

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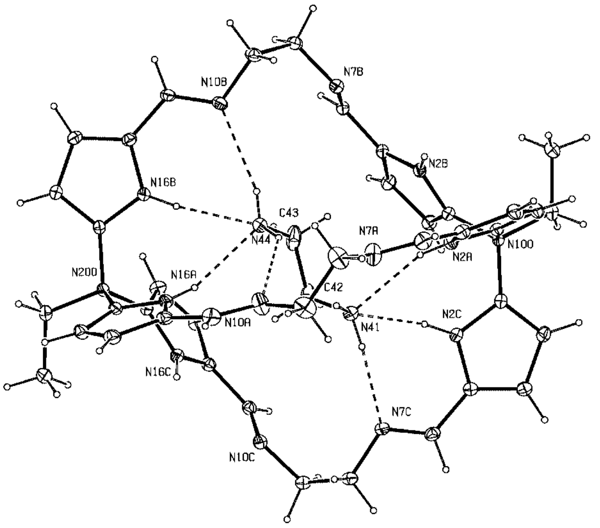

Fig. 2 The structure of **6·en**. Ellipsoids are shown at 10% probability. The 7 hydrogen bonds are shown as dotted lines. Distances for donor hydrogen bonds from the guest are N(41)···N(7c), 3.20; N(44)···N(10b), 3.17; N(44)···N(10a), 3.29 and acceptor hydrogen bonds are N(41)–N(2C), 3.05; N(41)–N(2a), 3.06; N(44)–N(16a), 3.04 and N(44)–N(16b), 3.06 Å.

acceptor interactions to the pyrrole nitrogen atoms and donor interactions to the Schiff base nitrogens. There are seven typical hydrogen bonding N··N distances which range between 2.99 and 3.22 Å (see Fig. 1). In the crystal structure of **7·bn** only two of the three pyrrole moieties at each end of the macrocycle are orientated with their NHs towards the guest **bn**. The remaining two pyrroles are both turned away and only participate in the binding interaction with the **bn** through weak C–$H_{bn}\cdots\pi_{pyrrole}$ contacts at 2.97 and 2.66 Å. Interestingly, in order to fit into the cavity the guest molecule **bn** takes up a *gauche, gauche, trans* conformation rather than the more energetically favourable *trans, trans, trans* conformation. Overall, inspection of the **7·bn** complex illustrates the excellent complementarity of the host's shape and hydrogen bonding capabilities which hold the guest in place through multiple co-operative binding interactions.

Further evidence for the binding of **bn** by **7** was provided by ^{1}H and ^{13}C NMR in $CDCl_3$ solution.[12] In the ^{1}H NMR spectrum of **7·bn** the two resonances for the methylene chain of the coordinated **bn** were observed to be shifted upfield, at δ 2.24 and 0.92 compared to their unbound values, 2.72 and 1.42 ppm. Peaks at δ 40.2 and 29.9 ppm in the ^{13}C of **7·bn** are assigned to the methylene carbons of the guest **bn**. The inclusion and identity of the guest was further qualified by ^{1}H COSY and ^{1}H–^{13}C HETCOR experiments. A very broad resonance at approximately δ 5 is attributed to both the pyrrolic and **bn** amine protons; this peak is lost upon addition of D_2O.

In a similar manner the preparation of **6** in THF produced the ethane-1,2-diamine (**en**) included complex **6·en**. The crystal structure of which was also determined and is shown in Fig. 2. The structure of **6·en** closely resembles that of **7·bn** with very similar hydrogen-bonding distances from the host's donor pyrrole and acceptor Schiff base nitrogen atoms to the guest **en**. Notably, the bound guest **en** adopts the *gauche* conformation. Weak contacts attributable to C–$H_{en}\cdots\pi_{pyrrole}$ interactions are again observed. The identity of the guest was supported by ^{1}H, ^{13}C and 2D NMR experiments with the incarcerated **en** molecule assigned to resonances at δ 2.12 (^{1}H), and 43.6 ppm (^{13}C).

The inclusion of the reactant diamine inside the Schiff base suggests that the formation of the tripyrrolyl cages is templated by the diamine. The preparation of **6** and **7** was performed in acetonitrile using 2 eq. but again yielded **6·en** (81%) and **7·bn** (73%). It is noteworthy that using 2 eq. of diamine does significantly improve the yield of tripyrrolyl cryptands. Considering the high yields of cages **6** and **7** it is quite likely that the guest diamine is involved, in some shape or form, in templating the formation of the bis(tripyrrolyl) cryptands.

The guest **en** could be simply removed from **6·en** by stirring with MeOH. ^{1}H NMR titration experiments in $CDCl_3$ of the diamine-free bis(tripyrrolyl) cryptand **6** were performed to confirm diamine binding and determine a stability constant. Titration of **en** with **6** produced identical ^{1}H, ^{13}C and 2D NMR spectra as for **6·en** and a binding constant, *K*, of 1500 ± 140 M^{-1} was calculated using EQNMR.[13]† Titration experiments showed **6** binds ethane-1,2-diol (**eg**) strongly, $K = 1060 \pm 29\ M^{-1}$; the resonance attributed to the **eg** methylene protons being shifted upfield from 3.74 to 3.32 ppm. However, no significant shift in the resonance of the methylene protons of 1,2-ethanedithiol (**es**) was observed under the same titration conditions. That no binding was observed for **es** can be attributed to a number of factors such as the reduced hydrogen bonding abilities of thiols, the larger size of the dithiol guest and the significantly lower stability of the *gauche* conformation in **es** compared to **en** and **eg**. Macrocyclic calix[4]pyrroles have been shown to bind neutral guest molecules in d_6-benzene solution.[12] The large binding constants for the binding of difunctional neutral guest molecules by the pyrrole cryptands reported here demonstrates the enhancement in molecular recognition that can be achieved by the use of three dimensional host molecules that encompass their guest. Further studies with neutral guest molecules are in progress.

In summary, bis(tripyrrolyl) cryptand-like cages have been prepared in excellent yields and preliminary studies demonstrate neutral guest molecule binding. The ease and scale with which the formylated tripyrrolylalkanes can be prepared offers plenty of opportunity for the future exploitation of these building blocks in the construction of new cryptands. We are currently exploring the cation and anion coordination chemistry of these bis(tripyrrolyl) cryptands and routes to further cages based on metal-assembled strategies.[14]

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Notes and references

‡ *Crystal data* for **7·bn**: $C_{50.5}H_{72}ClN_{16}O_{0.5}$, *M* 946.69, triclinic, space group $P\bar{1}$, $a = 10.955(12)$, $b = 14.307(17)$, $c = 17.45(2)$ Å, $\alpha = 100.85(1)$, $\beta = 99.17(1)$, $\gamma = 91.80(1)°$, $U = 2646$ Å^3, $Z = 2$, $\mu = 0.123\ mm^{-1}$, l = 1.184 gm cm^{-3}. **6·en**: $C_{44}H_{54}N_{14}$, *M* 779.02, triclinic, space group $P\bar{1}$, $a = 11.983(15)$, $b = 13.283(15)$, $c = 14.765(17)$ Å, $\alpha = 72.41(1)$, $\beta = 81.74(1)$, $\gamma = 77.62(1)°$, $U = 2180$ Å^3, $Z = 2$, $\mu = 0.075\ mm^{-1}$, l = 1.187 gm cm^{-3} . CCDC 167338, 167339. See http://www.rsc.org/suppdata/cc/b1/b104077b/ for crystallographic data in CIF or other format. The structures were refined on F^2 using SHELXL[15] to respectively *R*1 0.0881, *wR*2 0.2231 for 4360 reflections and *R*1 0.0756, *wR*2 0.2107 for 3602 reflections with $I > 2\sigma(I)$.

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