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Self-organization of dipyridylcalix[4]pyrrole into a supramolecular cage for dicarboxylate†

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Cis- and *trans*-dipyridylcalix[4]pyrroles were synthesized and *cis*-dipyridylcalix[4]pyrrole formed a supramolecular cage upon dimerization and coordination with Pd(II). The cage molecule recognised substrate selectively by hydrogen bonding to the two calix[4]pyrroles.

Anion recognition has attracted much attention in the field of supramolecular chemistry,¹ and its potential for medical and environmental applications has particularly focused attention on the development of sensors and approaches for removing specific anionic species. In 1996, Sessler *et al.* reported anion recognition by calix[4]pyrrole upon the hydrogen bonding of four NH pyrrolic protons.² Fluorescent anion sensors³ and colourimetric anion sensors⁴ employing functionally derivatised calix[4]pyrrole skeletons also have been reported. Lee *et al.* reported strapped calix[4]pyrroles⁵ exhibiting improved anion selectivity arising from the strap moiety recognizing the shape and size of the anion. For example, strapped calix[4]pyrrole is selective for chloride because chloride fits into the cavity formed by the strap. Improved selectivity for halide anions such as fluoride, chloride, and bromide have been reported by changing the length of the strap⁶ or by introducing an amide group into the strap moiety.⁷ These calix[4]pyrrole-based anion receptors mainly recognize halide anions. The recognition of a large anion such as ATP, ADP, or dicarboxylates requires a large recognition site. To date, calix[4]pyrrole dimers connected by a diethyl group have been reported as potential anion receptors,^{8,9} but their multi-step synthesis provides low yields. In this study, we report a new cage molecule consisting of a supramolecular dimer of dipyridylcalix[4]pyrrole¹⁰ (Fig. 1). This cage molecule is expected to form an approximately 10 Å cavity and anion

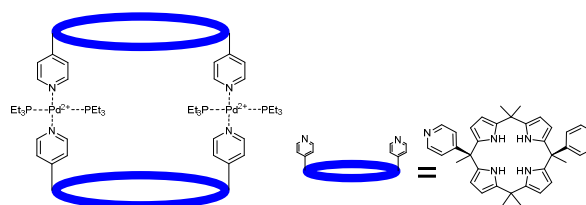


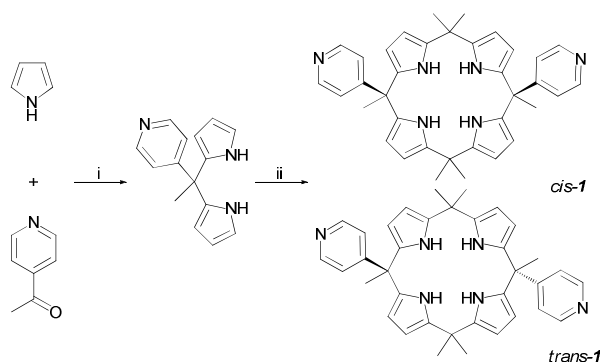
Fig. 1 Proposed structure of the supramolecular cage via metal coordination of dipyridylcalix[4]pyrrole.

recognition site by self-organisation via coordination to palladium(II) ion. This cage molecule is easy to synthesize via coordination to a metal ion and should exhibit ditopic recognition for a specific dianion.

The precursor of dipyridylcalix[4]pyrrole, 1-pyridyl-1-dipyrroethane, was synthesized from pyrrole and 4-acetylpyridine (Scheme 1). The mixture was stirred in hydrochloric acid. Neutralization with sodium bicarbonate resulted in the precipitation of 1-pyridyl-1-dipyrroethane, which was then dried *in vacuo*. The residue was purified by silica column chromatography (19%), dried, then dissolved in acetone. $\text{BF}_3 \cdot \text{OEt}_2$ was added to the solution and the mixture was stirred for 24 h. Two isomers (*cis*-**1**, *trans*-**1**) of 5,15-dipyridyl-5',10,10',15',20,20'-hexamethylcalix[4]pyrrole were separated by silica column chromatography (eluent; chloroform : ethyl acetate = 1 : 2) (γ = 9% (Rf 0.23), γ = 24% (Rf 0.33)) (Scheme 1). The two isomers (Rf 0.23 and Rf 0.33) gave similar ¹H NMR spectra, making it difficult to distinguish between the *cis* and *trans* forms. Crystals of the two isomers were obtained by slow evaporation using a mixed solvent of chloroform and acetone (or ethyl acetate) (Fig. 2), then X-ray crystal analysis was performed to determine the structures of the two isomers.

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†Electronic Supplementary Information (ESI) available: Synthetic procedures, ¹H NMR titration experiments, Job plots, ESI mass spectra, and X-ray crystal structures. See DOI: 10.1039/c000000x/



Scheme 1 Reagent and conditions: i, HCl, water, rt, 2 h; ii, $\text{BF}_3 \cdot \text{OEt}_2$, acetone, rt, 24 h.

X-ray crystallographic analysis (Fig. 2) indicated that Rf 0.23 and Rf 0.33 corresponded to *cis*-1 and *trans*-1, respectively. Interestingly, the crystal structure of *cis*-1 adopted a dimeric structure by hydrogen bonding *via* water molecules, specifically, hydrogen bonds between the oxygen atom of a water molecule and the two NH pyrrolic protons of calix[4]pyrrole, and a hydrogen bond between a hydrogen atom of a water molecule and the nitrogen atom of pyridine. As a result, the crystal structure of *trans*-1 was organised into a polymeric structure. *Cis*-1 was dissolved in dichloromethane, $\text{Pd}^{\text{II}}(\text{OTf})_2(\text{PEt}_3)_2$ was added (1.0 equiv.), and the mixture was stirred at room temperature. The pyridyl group is known to coordinate to Pd(II) in the *trans* position^{11,12} by reaction with *trans*- $\text{Pd}^{\text{II}}(\text{OTf})_2(\text{PEt}_3)_2$. The cage structure is likely formed by spontaneous dimerization and self-organisation (Scheme 2). The formation of the Pd complex was confirmed by ^1H NMR spectroscopy by dissolving *cis*-1 in acetonitrile- d_3 and adding the palladium reagent dropwise. The signal of the NH protons at 7.8 ppm were shifted upfield to 7.7 ppm (a) upon formation of the cage molecule **2**, the signals of the pyridine protons at 8.4 ppm and 6.8 ppm were shifted downfield to 8.6 ppm (b) and 7.0 ppm (c), respectively, and the signals of the β pyrrolic protons at 5.8 ppm and 5.6 ppm were shifted to 5.9 ppm (d) and 5.3 ppm (e), respectively. These shifts are believed to be due to coordination of the pyridine moieties to palladium(II) and showed that the pyridine moieties were affected by the cationic charge. Furthermore, the significant upfield shift of the β pyrrolic protons (e) of the cage molecule **2** seemed to

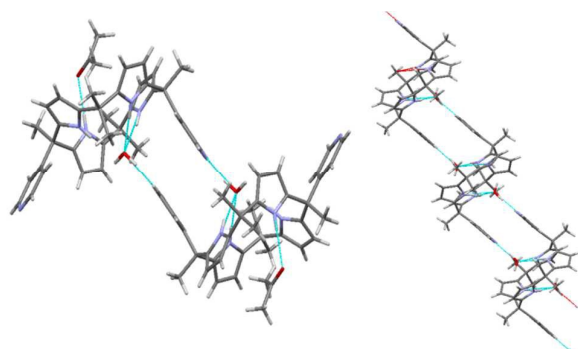
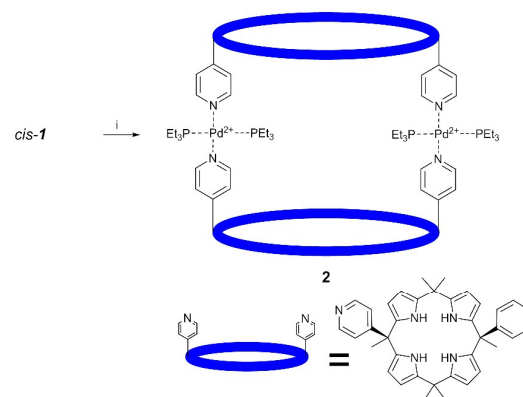


Fig. 2 Crystal structures of dipyridylcalix[4]pyrroles (Left: *cis*-1, Right: *trans*-1).



Scheme 2 Reagent and conditions: i, $\text{Pd}^{\text{II}}(\text{OTf})_2(\text{PEt}_3)_2$, CH_2Cl_2 , rt, 5 min.

result from the influence of the ring current of the pyridine moieties upon conformational change to the 1,3- (or 1,2-) alternative structure.¹ ^1H NMR titration experiments were performed using dicarboxylates ($-\text{O}_2\text{C}(\text{CH}_2)_n\text{CO}_2-$) with different carbon numbers dissolved in acetonitrile- d_3 to see if the cage molecule **2** can recognise a specific anion. First, **2** (2 mM) was titrated with tetrabutylammonium suberate ($n = 6$) (Fig. 3). The signal of the NH protons of **2** at 7.7 ppm (a) diminished during the titration and a new signal appeared at 8.0 ppm (a'). The intensity of the new signal was increased by further addition of the guest molecule (up to 0.8 equiv.).¹³ This result indicated that the cage molecule **2** recognised the suberate inside the cage at a slow exchange rate. The signal of the pyridine moiety changed from 8.6 ppm (b) and 7.0 ppm (c) to 8.4 ppm (b') and 6.9 ppm (c'), respectively, and the β pyrrolic protons at 5.9 ppm (d) and 5.3 ppm (e) changed to 5.8 ppm (d') and 5.6 ppm (e'), respectively. These results suggested that the cage molecule **2** with suberate adopted a cone structure that was in equilibrium between the cone and the 1,3- (or 1,2-) alternative structure (Fig. 3).

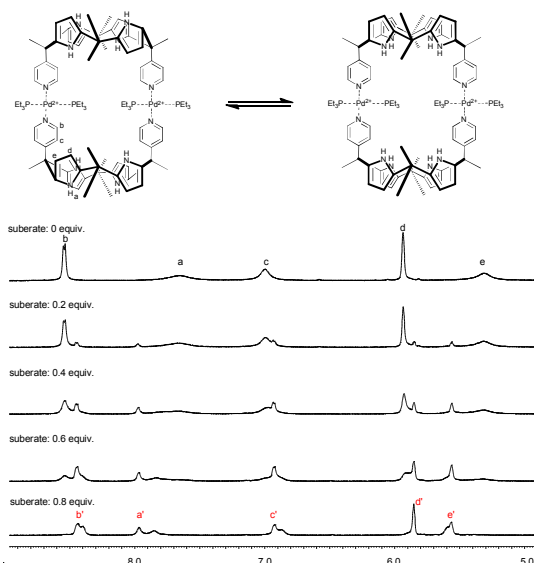


Fig. 3 ^1H NMR titration experiments of the cage molecule **2** with suberate (400 MHz, CD_3CN).

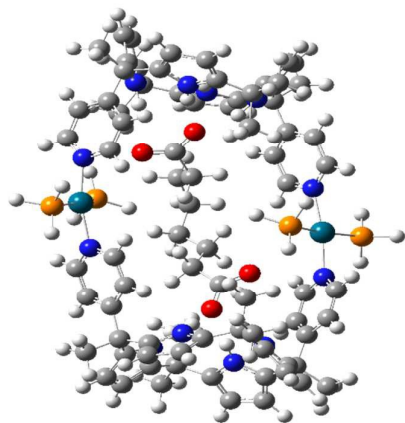


Fig. 4 Optimised structure of compound **2** with suberate obtained by CAM-B3LYP calculation using GAUSSIAN09¹⁵ (LanL2DZ for Pd, and 6-31G** for other atoms). To simplify the calculation, PH₃ was used instead of PEt₃.

Titration with tetrabutylammonium azelate ($n = 7$) resulted in spectral changes similar to that observed with suberate, suggesting that azelate was also incorporated inside the cage **2**. In contrast, titration with tetrabutylammonium pimelate ($n = 5$) gave different spectral changes from those with suberate or azelate. No signal at 8.0 ppm due to NH protons was observed. It suggested that pimelate was not incorporated into the cage **2**. The addition of tetrabutylammonium adipate ($n = 4$) provided similar spectral changes to that with pimelate. Taken together, the titration results indicate that dicarboxylates containing eight or nine carbons were recognised inside the cage **2**, whereas dicarboxylates with less than eight carbons were not recognised. Titration with acetate was performed as a control experiment. Up to one equivalent was incorporated inside the cage at a slow exchange rate, but the addition of more than 2 equivalents caused the peak shifts because extra acetate interacted with NH protons from outside the cage at a fast exchange rate. Job plots of the cage molecule **2** with suberate ($n = 6$) and azelate ($n = 7$) provided a maximum at 0.5 for suberate, indicating a 1:1 complex, whereas azelate provided a maximum at 0.7, indicating a 2:1 (host:guest) complex mainly (See ESI for details). Consequently, the slightly longer carbon chain of azelate was poorly recognised at the calix[4]pyrrole dimer recognition site, demonstrating that suberate was recognised selectively.¹⁴ Theoretical calculations¹⁵ indicated that suberate stabilized the complex because the size of this dianion fits the cage cavity (ca. 10 Å) (Fig. 4).

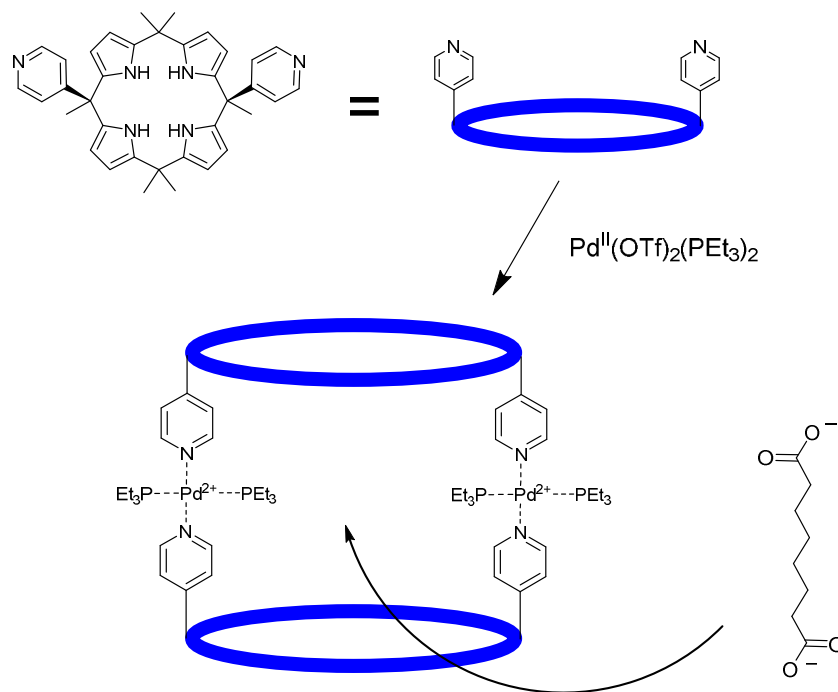
In conclusion, we have synthesized and isolated the *cis* and *trans* isomers of dipyrildylcalix[4]pyrrole. *Cis*-**1** easily formed a cage molecule by self-organization by reacting with palladium reagent. The cage molecule **2** recognised suberate selectively, formed a 1:1 complex, and was stabilized. Theoretical calculations showed that suberate ($n = 6$) fit the cavity of the cage molecule.

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Notes and references

- J. L. Sessler, P. Gale and W.-S. Cho, *Anion Receptor Chemistry*, The Royal Society of Chemistry, 2006.
- P. A. Gale, J. L. Sessler, V. Kral and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140–5141.
- H. Miyaji, P. Anzenbacher Jr, J. L. Sessler, E. R. Bleasdale and P. A. Gale, *Chem. Commun.*, 1999, 1723–1724.
- H. Miyaji, W. Sato and J. L. Sessler, *Angew. Chem. Int. Ed.*, 2000, **39**, 1777–1780.
- D. W. Yoon, H. Hwang and C. H. Lee, *Angew. Chem. Int. Ed.*, 2002, **41**, 1757–1759.
- C. H. Lee, H. K. Na, D. W. Yoon, D. H. Won, W. S. Cho, V. M. Lynch, S. V. Shevchuk and J. L. Sessler, *J. Am. Chem. Soc.*, 2003, **125**, 7301–7306.
- C. H. Lee, J. S. Lee, H. K. Na, D. W. Yoon, H. Miyaji, W. S. Cho and J. L. Sessler, *J. Org. Chem.*, 2005, **70**, 2067–2074.
- W. Sato, H. Miyaji and J. L. Sessler, *Tetrahedron Lett.*, 2000, **41**, 6731–6736.
- V. Valderrey, E. C. Escudero-Adán and P. Ballester, *Angew. Chem. Int. Ed.*, 2013, **52**, 6898–902.
- To our knowledge, the synthesis of dipyrildylcalix[4]pyrrole was first reported by N. Kiriya and H. Miyaji at the 91st Annual Meeting of the Chemical Society of Japan, Yokohama, March, 2011, Abstr., 1PA-083. Recently, its synthesis by other groups has also been reported. See: L. Adriaenssens, A. Frontera, D. Quin, E. C. Escudero-ada and P. Ballester, *J. Am. Chem. Soc.*, 2014, **136**, 3208–3218; P. Sokkalingam, D. S. Kim, H. Hwang, J. L. Sessler, C. H. Lee, *Chem. Sci.*, 2012, **3**, 1819–1824.
- J. Kim, D. Ryu, Y. Sei, K. Yamaguchi and K. H. Ahn, *Chem. Commun.*, 2006, 1136–1138.
- S. Ghosh and P. S. Mukh, *Dalton Trans.*, 2007, 2542–2546.
- The addition of one or more equiv. of suberate resulted in the spectra becoming complicated due to the appearance of new peaks. To simplify the discussion, Fig. 3 shows spectra obtained at up to 0.8 equiv.
- Electron spray ionization (ESI+) mass spectra of **2** and the complex with suberate were also measured. The obtained spectra were consistent with the calculated values of the isotope pattern of cage **2** complexed with Pd and suberic acid (See ESI).
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, *et al.*, Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, 2010.

Graphical abstract:



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