Cite this: Chem. Commun., 2012, 48, 8060-8062

www.rsc.org/chemcomm

## COMMUNICATION

## Calix[4]pyrroles bearing proximally *meso-meso* linking straps: synthesis and anion binding properties<sup>†</sup>

Ja-Young Park,<sup>*a*</sup> Kamil Skonieczny,<sup>*b*</sup> Naoki Aratani,<sup>*c*</sup> Atsuhiro Osuka,<sup>*c*</sup> Daniel T. Gryko\*<sup>*b*</sup> and Chang-Hee Lee\*<sup>*a*</sup>

Received 30th March 2012, Accepted 11th June 2012 DOI: 10.1039/c2cc33537a

Calix[4]pyrroles bearing two proximally crossing straps on the same or the opposite sides have been synthesized for the first time. The doubly *cis*-strapped compound exhibited highly cooperative six-point hydrogen bonding interactions with the anion involving both pyrrolic N–Hs and Ar–Hs.

The design and synthesis of neutral anion receptors with high affinity and selectivity for a variety of targeted anions represents a significant challenge in supramolecular chemistry. The use of hydrogen bonding interactions as recognition motifs for specific anions has been studied extensively because of the potential applications of the technologies in biological and environmental sciences.<sup>1</sup> Applications that have received particular interest in recent years include ion selective electrodes, fluorescence chemosensors and electrochemical signaling devices.<sup>2</sup> The development of novel and more specifically functionalized receptors showing enhanced selectivity requires fine tuning of the interactions with targeted guest molecules. Although hydrogen bonding interactions are weak non-covalent interactions that are strongly affected by both pH and solvent, they are commonly used as the driving force in anion recognition. Thus, the effective design of anion receptors is more challenging than the design of the corresponding cation receptors.<sup>3</sup> Among the various anion recognition motifs reported in the literature,<sup>4</sup> calix[4]pyrroles, which are readily accessible from the condensation of pyrrole and ketones, have been identified as versatile hosts for anion recognition and for halide anions especially.<sup>5</sup> We have reported several strapped calix[4]pyrroles as new homologues for anion-binding and ion-pair recognition motifs.<sup>6</sup> Threedimensional cyclic oligopyrroles have been reported by several groups engaged in research aimed at improving anion binding affinity and selectivity.<sup>7</sup> It is envisaged that calix[4]pyrroles bearing pre-organized and flexible binding domains will exhibit enhanced affinity and selectivity.

As part of our ongoing efforts to develop versatile receptors based on the strapped calix[4]pyrroles, we herein report the first example of a new class of calix[4]pyrroles, including compounds **1** and **2**, bearing proximal double straps on either side of the parent macrocycle (Scheme 1). The solid-state structures and anion binding behaviors of these doubly strapped calix[4]pyrroles are also reported. It was envisaged that the introduction of a flexible strap enabling the isolation of the binding domain by encapsulation would provide additional hydrogen bonding donor sites and potentially allow for specific modulation of the straps would enhance affinity and selectivity.<sup>8</sup> Moreover, the use of a hydrophobic cavity surrounded by the four alkyl groups could enhance the selectivity for hydrophobic anions.‡

Our original intention was to synthesize desired receptor 3, which bears diametrically crossing straps on the top and bottom sides of the macrocycle, *via* direct condensation of pyrrole and bis-ketone 4. However, the attempted condensation under various conditions failed to give desired product 3. It was envisaged that compound 3 would display multiple anion-binding properties with an especially high affinity for sphere shape anions. Compound 4 was synthesized over three steps (Scheme 2). The acid catalyzed condensation of bis-ketone 4 with pyrrole afforded bis-dipyrromethane 5 in 52% yield. Subsequent BF<sub>3</sub> mediated condensation of bis-dipyrromethane



Scheme 1 Calix[4]pyrroles bearing proximally *meso-meso* linking straps (1 and 2) and distally *meso-meso* linking straps (3).

<sup>&</sup>lt;sup>a</sup> Department of Chemistry and Institute of Molecular Science & Fusion technology, Kangwon National University,

Chun-Chon 200-701, Korea. E-mail: chhlee@kangwon.ac.kr <sup>b</sup> Institute of Organic Chemistry Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland. E-mail: danielteryko@gmail.com

<sup>&</sup>lt;sup>c</sup> Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan. E-mail: osuka@kuchem.kyoto-u.ac.jp

<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Synthetic details of all the compounds, spectroscopic data and single crystal X-ray data. CCDC 872113 (1) and 872114 (2). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/ c2cc33537a



Scheme 2 Synthesis of compounds 1, 2 and 6.

**5** with bis-ketone **4** unexpectedly afforded a mixture of products, including **1**, **2** and **6** in yields of 3%, 2% and 10%, respectively. However, compound **3** which is expected to form was not isolated.

Mechanistically, it was envisaged that the formation of compound 6 must be associated with an acid-catalyzed cleavage of the pyrrole-carbon bond in bis-dipyrromethane 5 affording a carbocationic intermediate, which underwent intramolecular nucleophilic attack by a neighboring pyrrole. Subsequent condensation of 6 with bis-ketone 4 with released pyrrole could afford either compound 1 or 2. To the best of our knowledge, compounds 1 and 2 are unprecedented in the literature. The structures were confirmed by X-ray diffraction analysis, which was performed on single crystals obtained by slow evaporation of the compounds from a mixture of chloroform and hexanes.

Single crystal X-ray crystallographic analysis of compounds **1** and **2** revealed that the two compounds adopted completely different geometries in the solid state.<sup>9</sup> The conformation of *cis*-doubly strapped compound **1** adopted a near perfect 1,3-alternate form, whereas the *trans*-doubly strapped compound **2** adopted a partial cone conformation (Fig. 1).

Consideration of the partial cone structure of compound **2** (Fig. 1(b)) revealed that two pyrrolic N–Hs were involved in an intramolecular hydrogen bonding interaction with two of the phenolic oxygens. The observed distance between  $N^2$  and  $O^2$  was 3.125 Å and  $N^1$  and  $O^3$  was 3.255 Å. The scoop-like solid state conformation of compound **2** was also reflected in solution NMR.

Intramolecular hydrogen bonding of the two pyrrolic N–Hs appeared clearly at 8.69 ppm in the <sup>1</sup>H NMR spectra, whereas the other two non-hydrogen bonding pyrrolic N–Hs appeared



Fig. 1 Single crystal X-ray structures of receptors 1 (a) and 2 (b). The hydrogen atoms have been removed for clarity. Two of the pyrrole N–Hs and two of the phenolic oxygen atoms on the strap form hydrogen bonding interactions (b). The displacement ellipsoids have been scaled to the 50% probability level.



Fig. 2 300 MHz  $^{1}$ H NMR spectra of compounds 2 (top) and 1 (bottom) in CDCl<sub>3</sub>.

at 7.05 ppm (Fig. 2). The anion binding behavior of compounds 1 and 2 in acetonitrile was studied by <sup>1</sup>H NMR spectroscopy. The slow nature of the complexation-decomplexation equilibrium enabled direct observation of the binding process. Quantitative binding studies with fluoride and chloride anions revealed distinctive changes in the chemical shifts of all the proton signals (ESI<sup>†</sup>). Two singlets corresponding to the N-H resonances in compound 1 that appeared at 6.99 and 6.82 ppm were shifted to  $\sim 13.24$  ppm following the addition of fluoride anions and subsequently appeared as a pair of doublets. This splitting of the pyrrolic N-H resonances to two sets of doublets reflects the anisochronic nature of the complex (Fig. 3).<sup>10</sup> The  $\beta$ -pyrrolic resonances that originally appeared as two singlets at 5.87 and 5.84 ppm were also shifted to 5.63 and 5.60 ppm, respectively, upon addition of the fluoride anion. The resonance of the inner Ar-H on the strap that originally appeared at 6.0 ppm was shifted to 6.37 ppm upon addition of a fluoride anion, which was consistent with the presence of a weak hydrogen bonding interaction between the Ar-H bond and the fluoride anion. A slight shift down-field of the methylene proton next to the phenolic oxygen also indicated the presence of a weak hydrogen bonding interaction.

In contrast, receptor **1** exhibited a fast complexationdecomplexation equilibrium process with chloride anions (Fig. 4). Anion-dependent shifts were observed in all of the signals. The pyrrolic N–H resonances were shifted to 11.12 ppm and appeared as a broad singlet. The inner Ar–H resonance on the strap was shifted to 6.62 ppm upon saturation. The inner Ar–H exhibited a slight down field shift following fluoride binding. These results provide support for the contention that the chloride anion forms stronger hydrogen bonding interactions



Fig. 3 Changes in the <sup>1</sup>H NMR spectra of receptor 1 following the addition of fluoride anions (as its tetrabutyl ammonium salt) in  $CDCl_3$ .



Fig. 4 Changes in the  ${}^{1}H$  NMR spectra of receptor 2 following the addition of fluoride anions (as its tetrabutyl ammonium salt) in CDCl<sub>3</sub>.

with the inner Ar-H than the fluoride anion. The larger size of chloride anions provides a rational basis for this conclusion. <sup>1</sup>H NMR spectral titration indicated that the smaller and more electronegative fluoride anion formed tighter hydrogen bonding interactions with the pyrrolic N-Hs and looser interactions with the Ar-Hs. In contrast, the relatively larger and less electronegative chloride anion formed loose hydrogen bonding interactions with the pyrrolic N–Hs and stronger interactions with the Ar–Hs. No appreciable binding interactions were observed with other anions such as bromide, iodide, sulfate or dihydrogen phosphate. To determine the energetics associated with the formation of the receptor-anion complexes, isothermal titration calorimetry (ITC) measurements were performed in acetonitrile. Unfortunately, the calorimetric traces for the fluoride anions did not show proper curve fitting. In contrast, traces for the chloride anions revealed progressive changes in the heat pulse and showed proper curve fitting.

The binding isotherm obtained for the binding of receptor 1 with Cl<sup>-</sup> revealed clean exothermic equimolar binding for the formation of the corresponding complexes. Interestingly, the affinity constant for the formation of  $[1 \cdot Cl^-]$  ( $K = 2.65 \times 10^5 \text{ M}^{-1}$ ) was ten times larger than that for the formation of  $[2 \cdot Cl^-]$ ( $K = 2.31 \times 10^4 \text{ M}^{-1}$ ), clearly indicating the cooperative binding of the two Ar–Hs with the chloride anion in receptor 1 (ESI†). The highly selective binding of receptor 1 with fluoride anions indicates that the double strapping of the calix[4]pyrrole macrocycle induces high selectivity toward smaller anions such as fluoride and chloride anions. The driving force for the enhanced binding was considered to be a combination of the C–H–X<sup>-</sup> and N–H–X<sup>-</sup> hydrogen bonding interactions. The introduction of multiple straps also reduced the matrix–guest interaction by isolation of the binding domain.

In conclusion, doubly strapped calix[4]pyrroles have been successfully synthesized and characterized for the first time. The current receptor systems support the concept of designer anion receptors used for the recognition of smaller anions with high affinity and selectivity. The approach detailed within this report provides a novel and useful complementary tool to other affinity modulation techniques currently being pursued in the context of supramolecular calix[4]pyyrrole-based anion binding chemistry.

We are grateful for support received from the Basic Science Research Program through the NRF (2009-0087013). We also acknowledge the Central Instrumentation Facility at KNU and BK21 program for support. D.T.G. thanks the Polish Ministry of Science and Higher Education (Contract N204 123837).

## Notes and references

‡ X-ray summary for 1 and 2: crystals grew by slow evaporation from acetonitrile and diethyl ether.

- (a) P. Chakrabarti, J. Mol. Biol., 1993, 234, 463; (b) M. A. Van Kuijck, R. A. M. H. Van Aubel, A. E. Busch, F. Lang, G. M. Russel, R. J. M. Bindels, C. H. Van Os and P. M. T. Deen, Proc. Natl. Acad. Sci. U. S. A., 1996, 93, 5401; (c) B. J. Calnan, B. Tidor, S. Biancalana, D. Hudson and A. D. Frankel, Science, 1991, 252, 1167.
- 2 (a) A. P. de Silva, H. Q. N. Guanarante, T. Gunnlaugson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515; (b) J. L. Sessler, *CHEMTECH*, 1999, **29**, 16.
- 3 (a) J. L. Sessler, A. Gebauer and P. A. Gale, *Gazz. Chim. Ital.*, 1997, **127**, 723; (b) J. L. Sessler, P. Anzenbacher, Jr., K. Jursikova, H. Miyaji, J. W. Genge, N. A. Tvermoes, W. E. Allen and J. A. Shriver, *Pure Appl. Chem.*, 1998, **70**, 2401.
- 4 (a) K. Kavallieratos, S. R. de Gala, D. J. Austin and R. H. Crabtree, J. Am. Chem. Soc., 1997, 119, 2325; (b) K. Kavallieratos, C. M. Bertao and R. H. Crabtree, J. Org. Chem., 1999, 64, 1675; (c) M. K. Chae, G.-Y. Cha and K.-S. Jeong, Tetrahedron Lett., 2006, 47, 8217; (d) J. M. Mahoney, A. M. Beatty and B. D. Smith, J. Am. Chem. Soc., 2001, 123, 5847; (e) M. J. Deetz, M. Shang and B. D. Smith, J. Am. Chem. Soc., 2000, 122, 6201; (f) Z. Rodriguez-Docampo, S. I. Pascu, S. Kubik and S. Otto, J. Am. Chem. Soc., 2006, 128, 11206; (g) S. O. Kang, D. Powell, V. W. Day and K. Bowman-James, Angew. Chem., Int. Ed., 2006, 45, 1921.
- 5 J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F. P. Schmidtchen, G. W. Bates, M. E. Light and P. A. Gale, *J. Am. Chem. Soc.*, 2006, **128**, 12281.
- 6 (a) H. Miyaji, H.-K. Kim, E.-K. Sim, C.-K. Lee, W.-S. Cho, J. L. Sessler and C.-H. Lee, J. Am. Chem. Soc., 2005, 127, 12510; (b) C.-H. Lee, H. Miyaji, D.-W. Yoon and J. L. Sessler, Chem. Commun., 2008, 24; (c) J. L. Sessler, S. K. Kim, D. E. Gross, C.-H. Lee, J.-S. Kim and V. M. Lynch, J. Am. Chem. Soc., 2008, 130, 13162; (d) J. Yoo, M.-S. Kim, S.-J. Hong, J. L. Sessler and C.-H. Lee, J. Org. Chem., 2009, 74, 1065; (e) S.-H. Kim, S.-J. Hong, J. Yoo, S. K. Kim, J. L. Sessler and C.-H. Lee, Org. Chem., 2009, 11, 3626; (f) D. E. Gross, D.-W. Yoon, V. M. Lynch, C.-H. Lee and J. L. Sessler, J. Inclusion Phenom. Macrocyclic Chem., 2010, 66, 81; (g) S. K. Kim, J. L. Sessler, D. E. Gross, C.-H. Lee, J.-S. Kim, V. M. Lynch, L. H. Delmau and B. P. Hay, J. Am. Chem. Soc., 2010, 132, 5827.
- 7 (a) S.-J. Hong, J. Yoo, D.-W. Yoon, J. Yoon, J. S. Kim and C.-H. Lee, *Chem.–Asian J.*, 2010, 5, 768; (b) C. Bucher, R. S. Zimmerman, V. M. Lynch and J. L. Sessler, *J. Am. Chem. Soc.*, 2001, 123, 9716.
- 8 (a) 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; (b) D. W. Yoon, H. Hwang and C. H. Lee, Angew. Chem., Int. Ed., 2002, 41, 1757.
- 9 X-ray data of a crystal having dimension of  $0.3 \times 0.3 \times 0.4$  mm were collected on a Nonius CAD4 mach 3 diffractometer equipped with graphite-monochromated MoKa radiation ( $\lambda = 0.71373$  Å) at room temperature. The unit cell was determined to be monoclinic,  $P2_{ijn}$  (no. 14), jZ = 4, a = 10.335(2), b = 16.519(3), c = 20.329(3)Å,  $\beta = 95.297(14)^\circ$ , V = 3455.9(9)Å<sup>3</sup>,  $\rho_{calc} = 1.243$  gcm<sup>-3</sup> on the basis of 25 reflections. A total of 7467 reflections were measured, 6990 unique ( $R_{int} = 0.0646$ ). The structure refined data  $F^2$  to  $R_w = 0.3248$ , R = 0.1013 (3162 reflections with  $F_o > 4\sigma F_o$ ), and  $G_oF = 1.125$  for 433 refined parameters. The data were collected by using the  $\omega$ -2 $\theta$  scan technique in the range 2.14°  $< \theta < 26.29^\circ$ . No absorption corrections were applied. The structure was solved by a direct method and refined by full matrix least square calculation with SHELXL-97. Anisotropic thermal parameters were used for all non-hydrogen atoms.
- 10 W. Sato, H. Miyaji and J. L. Sessler, *Tetrahedron Lett.*, 2000, 41, 6731.