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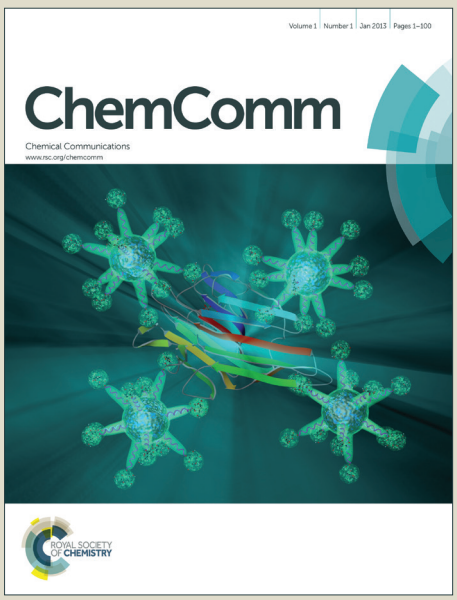

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Synthesis and anion binding studies of *o*-phenylenevinylene-bridged tetrapyrrolic macrocycle as an expanded analogue of calix[4]pyrrole†

Sudip Kumar Ghosh,[a] Masatoshi Ishida,[a,b] Jiazhu Li,[a] Won-Young Cha,[a] Vincent M. Lynch,[c] Dongho Kim,*[a] and Jonathan L. Sessler*[a,c]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An *o*-phenylenevinylene-bridged tetrapyrrolic macrocycle (2) was synthesized by means of a Horner–Wadsworth–Emmons reaction between benzylbisphosphonate and SEM-protected diformylpyrrole, followed by deprotection of the SEM groups. This conformationally flexible tetrapyrrole can be considered as an expanded calix[4]pyrrole analogue, which acts as a receptor for the chloride and bromide anions in THF-d_8, but undergoes deprotonation upon exposure to the fluoride anion.

Anions play significant roles in the biological, industrial and environmental processes.[1] Accordingly, the recognition of anionic species has emerged as a topic of foremost importance in supramolecular chemistry.[2] To date, a wide range of acyclic and macrocyclic receptors, both neutral and charged, have been synthesized and tested as anion receptors.[3] Among the various neutral organic anion receptors, *meso*-octamethylcalix[4]pyrrole (**1**) has received particular attention. This nonconjugated tetrapyrrolic macrocycle acts as an easy-to-synthesize host for anions, particularly halide anions, in organic media.[4] Calix[4]pyrrole **1** is flexible and undergoes a classic 1,3-alternate-to-cone conformational change upon anion binding. To improve the anion binding affinity and modulate the selectivity of the basic calix[4]pyrrole framework, many structural modifications (e.g., strapped calixpyrrole systems[5]) have been made. These improvements are thought to reflect, at least in part, structurally imposed reductions in the degree of conformational freedom. The use of three-dimensional calixpyrrole analogues has also been explored as a means for limiting flexibility and enhancing the degree of preorganization.[6] Less well explored are larger more flexible pyrrolic macrocycles where little effort has been made to achieve a good structural and geometric match with the targeted anionic substrates. It is thus an open question whether such systems would serve as anion receptors under conditions where **1** displays high affinities. In an effort to explore this issue, we report here the synthesis of a new *o*-phenylenevinylene-bridged tetrapyrrolic macrocycle (**2**) and its interactions with halide anions in organic media.

The crucial step in the synthesis of **2** is a Horner–Wadsworth–Emmons (HWE) reaction. This reaction, while well-studied in the context of, *inter alia*, creating alkene-functionalized porphyrin derivatives,[7] has not been used to our knowledge to create *de novo* oligopyrrolic macrocycles. In the present system, the *o*-phenylenevinylene- and *α,α'*-linked pyrrolic-subunits were connected via *trans*-alkene bridges by the HWE reaction. This was done by condensing the SEM-protected form of 2,5-diformylpyrrole (**4**) with tetraethyl(1,2-phenylene-bis-(methylene))bis(phosphonate) (**5**) under strongly basic conditions at reflux. Purification via silica gel column chromatography yielded three SEM-protected phenylene-pyrrole macrocycles (**3a-c**) confirmed by preliminary mass spectroscopy (Scheme 1). While macrocycle **3c** was found to be unstable under normal laboratory conditions, macrocycles **3a** and **3b** could be characterized by means of high-resolution mass spectrometric and ^{1}H NMR ($CDCl_3$) spectral analyses (Figs. S1-S3 in the ESI†).

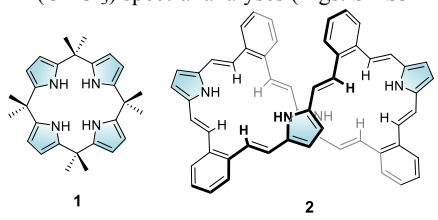
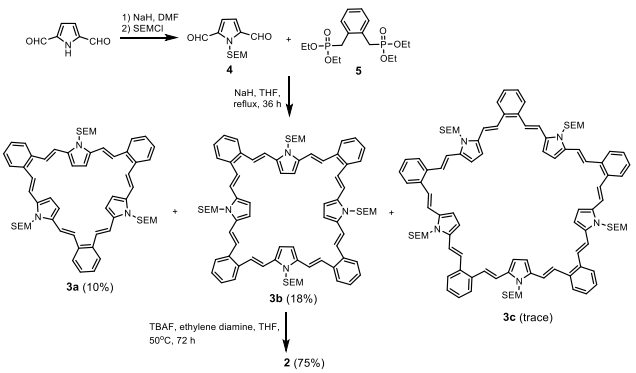


Fig. 1 *meso*-Octamethylcalix[4]pyrrole (**1**) and the *tetrakis*-(*o*-phenylenevinylene-pyrrole) macrocycle (**2**) used in this study.



Scheme 1 Synthesis of compounds **2** and **3a-c**.

The tetrapyrrolic macrocycle **2** was obtained by deprotection with tetrabutylammonium fluoride (TBAF) and ethylenediamine in THF at 50 °C.[8] Purification of **2** was carried out by preparative TLC and the purity of the sample was confirmed by HPLC analyses (Fig. S4). THF and DMSO were chosen for the latter studies due to the relatively poor solubility of **2** in $CDCl_3$.

Compound **2** was characterized by HR-mass spectrometry and NMR spectroscopy (Figs. S5-S8). The ^{1}H NMR spectrum of **2** in

THF-d_8 revealed a singlet at δ 10.66 ppm corresponding to the four pyrrolic NH resonances and the β-pyrrolic proton signals appeared as a doublet at 6.18 ppm at 298K. It should be noted that two sets of doublet signals at 6.77 and 7.09 ppm are assigned to the vinylenic protons with *trans*-conformation, respectively, as inferred from the relatively large coupling constants, $J > 16$ Hz. In the case of DMSO-d_6, less well-resolved spectral features were observed (Fig. S7). This was taken as evidence that **2** has a time averaged symmetric structure under conditions of the ^{1}H NMR analyses. The specific chemical shift values of **2**, particularly those of the pyrrole-NH protons (δ = 10.66 and 11.5 ppm in THF and DMSO, respectively) provide support for the conclusion that this ostensible hetero-polyene with a formal 40 π-electron periphery is nonaromatic. The UV-vis absorption (λ_{max} = 366, 400 and 414 nm) and strong fluorescence emission (λ_{em} = 561 nm, Φ_{FL} = 0.67) features are consistent with the proposed lack of extensive conjugation in **2** (Fig. S9). Moreover, no appreciable solvent or temperature dependence was found in the absorption spectra (Figs. S10-S11).

The three-dimensional structure of **2** was elucidated by single crystal X-ray diffraction analysis (Fig. 2). The figure eight-like nonplanar conformation was clearly seen in the solid state. This was further supported by the density functional theory (DFT) calculations performed at the B3LYP/6-31G(d) level. In the optimized structure of **2**, the twisted structure is 9.62 kcal/mol more stable than that of possible bowl-shaped curvature (Fig. S12). Presumably, this reflects a lack of global π-conjugated periphery in the case of **2**, a phenomenon that can be traced to the inherently deformed structure, which precludes effective π-orbital overlap.

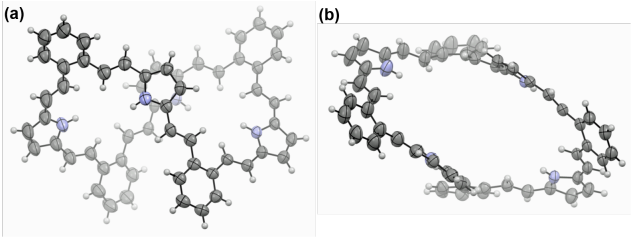


Fig. 2. Crystal structure of **2** (a, front view; b, side view). Thermal ellipsoids are shown at the 50% probability level. Co-crystallized solvent molecules are omitted for clarity.

In an effort to assess whether **2** would act as an anion receptor in analogy to calix[4]pyrrole **1**, its anion binding behaviour was studied in THF-d_8 using NMR and optical spectroscopies. Upon gradual addition of fluoride anion (as TBAF, up to 3 equiv), the aromatic CH signals were separated along with the slight shift of the original NH signal appeared at 10.66 ppm to the lower field region in the ^{1}H NMR spectrum (Fig. 3a-b and S13). These changes and new observation of another NH signal at 14.2 ppm are ascribed to fluoride anion binding with exchange kinetics that are slow on the NMR time scale.

In addition to the above spectral changes, a new very broad peak is observed around 15.3 ppm upon the addition of >3 equiv. of TBAF. This signal corresponds to the formation of bifluoride anion (HF_2^-). After the addition of 5 equiv. of TBAF, five sets of proton signals are seen in the 5.8 to 8.2 ppm spectral range along with disappearance of NH proton signals; this is consistent with the formation of a fully deprotonated, time-averaged symmetric form of **2** (Fig. 3c).[9] The formation of HF_2^- upon fluoride anion induced deprotonation[10] was also confirmed in the DMSO-d_6 solvent as inferred from the appearance of a characteristic triplet around 16 ppm in the ^{1}H NMR spectrum (Fig. S14) as well as the ^{19}F NMR signals at −152 (in THF-d_8) to −143 ppm (in DMSO-d_6) (Figs. S15-S16). Further support for the proposed deprotonation came from the observation of similar macrocycle-derived features in the ^{1}H NMR spectrum upon the addition of tetrabutylammonium hydroxide to **2** in THF-d_8 (Fig. S17).

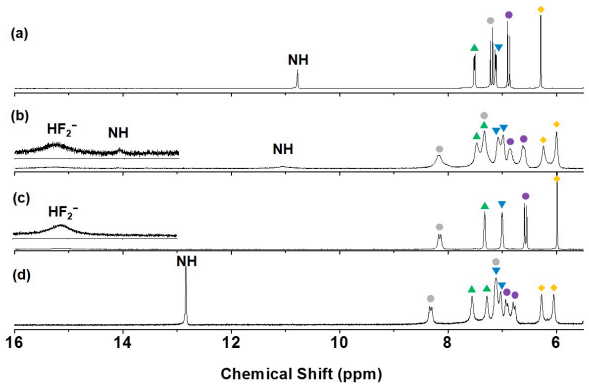


Fig. 3 ^{1}H NMR spectra of **2** in the presence of (a) 0 equiv, (b) 3 equiv and (c) 5 equiv. TBAF. The spectrum of **2** was obtained with addition of 4 equiv. of chloride. All spectra were recorded in THF-d_8 at 298 K.

The fluoride anion binding behaviour of **2** was also probed in THF via use of optical spectroscopy. Upon titration with TBAF, two different absorption profiles were observed depending on the relative anion / receptor ratios. Systematic changes with well-defined isosbestic points were observed upon addition of up to 2 equiv. of this fluoride anion source (Fig. 4). The subsequent addition of another 2 equiv. of TBAF led to a different set of spectral changes. The changes seen upon the addition of ≥ 2 equiv. of TBAF in THF are thought to reflect deprotonation of **2** along with the formation of HF_2^- anion. Consistent with this conclusion are the sharp changes in colour seen upon the addition of ≥2 equiv. of TBAF, with the solution turning from yellow to dark brown (Fig. S18). Accordingly, the relatively strong fluorescence of **2** is quenched in the presence of TBAF (Fig. S18). On this basis we conclude that macrocycle **2** is able to signal fluoride anion-induced deprotonation both via the unaided eye and by monitoring the fluorescence quenching.

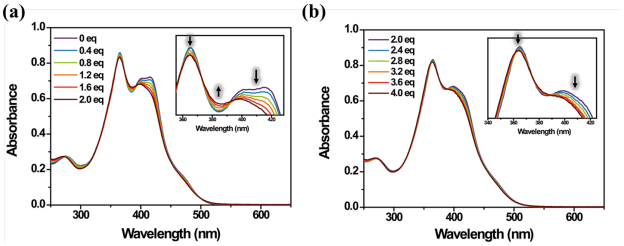


Fig. 4 UV-vis spectra recorded during the titration of a THF solution of **2** (10^{-5} M) with TBAF (a) 0-2 equiv. and (b) 2-4 equiv.

Macrocycle **2** also exhibited slow binding equilibria when treated with the other anions, such as chloride and bromide anions. These slow binding kinetics (on the NMR time scale)

precluded quantitative analyses using ^{1}H NMR spectral methods. Nevertheless, qualitative trends and insights into the nature of the presumed anion binding could be inferred. Upon treatment of **2** with TBACl in THF-d_8, a new pyrrolic NH resonance at 12.8 ppm was seen in the ^{1}H NMR spectrum (Fig. 3d and S19). This peak was observed in conjunction with the original NH signal at 10.66 ppm until the addition of 3 equiv. of chloride. In the presence of 4 or more equiv. of TBACl, all of the phenylene, *trans*-alkeneic and *β*-pyrrolic proton resonances are observed as two sets of signals as was seen in the initial binding studies involving fluoride (Fig 3b). All peaks except the NH proton signal are broadened. Taken in concert, these observations provide support for the suggestion that strong H-bonding interactions serve to bind the chloride to the pyrrolic subunits and that the macrocycle adopts a structure upon anion binding that is not time-average symmetric. Notably, the SEM-protected reference system, macrocycle **3b**, is unresponsive towards these anions. The binding affinity of **2** for chloride in THF was evaluated by means of a UV-Vis spectral titration, which gave a value for K_a of 2.75 × 10^4 M^{-1} with a good fit to a 1:1 binding profile being seen (Fig S20). This finding is consistent with the Job plot behaviour (Fig. S20b).

Analogous changes were observed when the interactions between **2** and TBABr were monitored by ^{1}H NMR spectroscopy (Fig. S21). However, in this case the signals seen in the presence of 4 equiv. of the anion were even broader, masking the putative signal splitting. The UV-Vis spectral titration curves could be fitted to give a smaller K_a value of 1.23 × 10^4 M^{-1} for bromide compared to that of chloride (Fig S22). Macrocycle **2** proved unresponsive to TBAI under similar conditions of study.

To allow comparisons with calixpyrrole **1**, analogous chloride anion binding studies were carried out in CH_2Cl_2 using TBACl (Fig. S23). This gave an equilibrium constant K_a = 4.26 × 10^4 M^{-1} for **2**, which is substantially larger than the value of 4.3 × 10^2 M^{-1} determined for **1** using this salt in this solvent.[4a] The relatively stronger chloride affinity seen for **2** as compared to **1** could reflect a system that can more readily undergo the conformational motions needed to complex a halide anion through NH hydrogen bonds than unstrapped calix[4]pyrroles, for which an energetically unfavourable 1,3-alternate to cone conversion is required prior to anion recognition. The larger size of **2** relative to **1** is also expected to favour the binding of the chloride anion, which is structurally less-well suited to interact with calix[4]pyrroles than the fluoride anion. Upon exposure to TBACl, the emission intensity of **2** was seen to increase with an hypsochromic shift in λ_{em} being observed (Fig. S20d).

The present findings provide support for the conclusion that non-preorganized analogues of calix[4]pyrrole can be prepared and that they act as effective chloride and bromide anion receptors in organic media. The *o*-phenylenevinylene-bridged pyrrolic macrocycle **2** of this study was found to bind the fluoride anion when the fluoride-to-receptor ratio was low. However, addition of more than 2 equiv. of fluoride led to spectroscopic and colour changes consistent with deprotonation, allowing for indirect anion sensing. We thus propose that flexible polypyrroles may have a role to play as anion sensors and receptors.

This work was supported by the U.S. National Science Foundation (CHE-1057904 to J.L.S.), the Robert A. Welch Foundation (F-1018 to J.L.S.), the Mid-carrier Researcher Program (2010-0029668 to D.K.) of the National Research Foundation grant funded by MEST-Korea, a Science and Technology Grant-in-Aid (No. 25888017 to M.I.) from the JSPS.

Notes and references

[a]*Department of Chemistry, Yonsei University, Seoul 120-749, Korea. Email: dongho@yonsei.ac.kr*
[b]*Education Center for Global Leaders in Molecular Systems for Devices, Kyushu University, Fukuoka 819-0395, Japan.*
[c]*Department of Chemistry, The University of Texas at Austin, Texas 78712-1224. United States. Email: sessler@cm.utexas.edu*

†Electronic Supplementary Information (ESI) available: Synthetic procedures, details of spectroscopic and calculational analyses, fitting of binding curves and X-ray crystallographic details; CCDC 983010. See DOI: 10.1039/b000000x/.

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TOC

An expanded analogue of calix[4]pyrrole with a flexible scaffold has been prepared; it acts as an effective anion receptor in organic media.