ORGANIC LETTERS

2013
Vol. 15, No. 2
306–309

Calix[2]bispyrrolylarenes: New Expanded Calix[4]pyrroles for Fluorometric Sensing of Anions via Extended π-Conjugation

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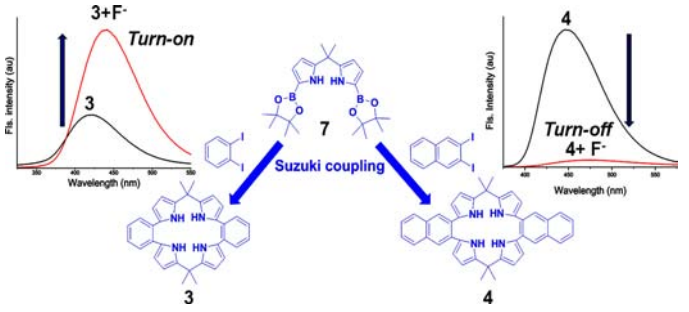
Received November 21, 2012

ABSTRACT



Two new expanded calix[4]pyrroles 3 and 4 were synthesized by '2 + 2' cyclocoupling of easily prepared diboryldipyrromethane 7 (by Ir-catalyzed CH-bond activation) with appropriate diiodoarenes using the Suzuki protocol. Owing to the unique design, both macrocycles exhibited extended π-conjugation and enhanced fluorescence. Upon complexation with anions (fluoride and acetate), receptor 3 displayed *turn-on* sensing of fluorescence, whereas 4 showed *turn-off* sensing.

Subsequent to the discovery of anion binding by calix[4]pyrrole, the challenge was to achieve needful manipulations so as to enhance the affinity and selectivity toward various anions to find potential applications of this tetrapyrrolic nonaromatic macrocycle.[1] Toward this end, the major emphasis has been on substitution at its periphery to enhance the strength of H-bonding,[2] attachment of a strap to increase preorganization,[3] and core expansion via either increasing the number of pyrrolic moieties (and hence number of H- bond donors)[4] or utilizing various spacers to increase the core size,[5] and as a consequence increasing the possibility to access larger anions. The latter strategy, while increasing the core size, also increased the option to

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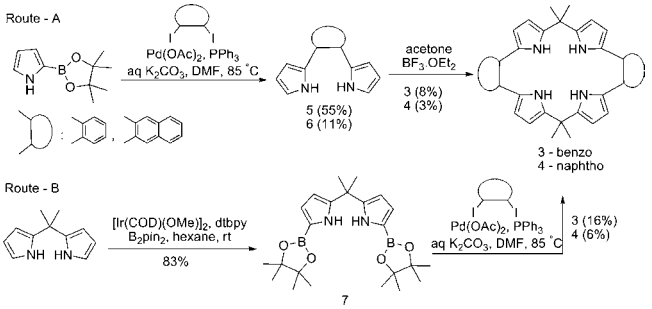
10.1021/ol3032158
Published on Web 12/26/2012

bring forth additional interactions such as aromatic CH-anion (receptor **1**) and intermolecular CH$\cdots\pi$ interactions to enhance binding affinity and/or selectivity.[5] In this direction, we have very recently demonstrated that incorporation of simple ethene moieties as spacers between two dipyrromethane units can lead to colorimetric sensing of fluoride ion via anion$-\pi$ interactions (receptor **2a**).[6] We envisaged that incorporation of a fluorescent probe as a spacer can further enhance the sensitivity of this type of system toward anions. In this regard, herein we report the synthesis of calix[2]bispyrrolylarenes **3** and **4**, two new expanded calix[4]pyrroles, and their anion binding properties in organic media. These macrocycles were synthesized in two steps by following two routes (Scheme 1). In route A, 2-borylpyrrole[7] was coupled with 1,2-diiodobenzene by the Suzuki protocol to obtain bispyrrolyl benzene **5** in 55% yield. However, the reaction with 2,3-diiodonaphthalene under the identical conditions gave **6** in only 11% yield (removal of naphthalene, probably obtained via deiodination, caused a major hindrance and reduced the yield).[8] Acid catalyzed condensation of **5** and **6** with acetone afforded macrocycles **3** and **4** in 8% and 3% yield respectively. However, isolation of the products (very closely associated with another spot in TLC) required rigorous chromatographic purification, reducing the yields, making reaction scaleup difficult. This led us to explore alternate synthetic routes. In this regard, the direct borylation of pyrrole at the α-position (employed in route A) appeared very attractive. Consequently, we redesigned our synthetic strategy according to route B. Here, the Ir-catalyzed C$-$H bond activation methodology[7] yielded the 2,2′-diboryldipyrromethane **7** in a single step from the corresponding dipyrromethane in very good yield (83%). Isolation of **7** was very easy as the product precipitated out from the reaction mixture and hence the reaction could be easily scaled up to make the desired precursor at gram scale. Subsequent '2 + 2' cyclocoupling of **7** with 1,2-diiodobenzene or 2,3-diiodonaphthalene, using the Suzuki protocol, led to formation of **3** and **4** as a single product in 16% and 6% yield respectively (route B).[8] Interestingly, unlike in the case of **1**, we did not observe the formation of higher macrocyclic analogues.[5] While Osuka et al. have used this borylation strategy extensively on porphyrins, to the best of our knowledge there is no report utilizing this methodology to prepare oligopyrrolic building blocks.[9] In particular, this is very useful in designing hosts for anions,

Scheme 1. Synthetic Protocol of Calix[2]bispyrrolylarenes



where selective α-halogenation of pyrrole mostly leads to polymerization in the absence of protecting groups or electron-withdrawing substituents at their β-positions; in contrast, the easily prepared alkylated derivatives drastically reduce their affinity for anions in the neutral state.[10] To our knowledge, this is the first report where the Suzuki protocol is utilized for the generation of macrocycles for host$-$guest chemistry (that are in general synthesized following acid catalyzed methodologies) and there are very few reports where this strategy is employed for porphyrinoid synthesis.[11] All the compounds were characterized by ^{1}H, ^{13}C NMR spectroscopy and mass analysis. Further, the solid state structure of **3** could also be elucidated by a single crystal X-ray diffraction method. The macrocycle adopts a 1,3-alternate conformation, and the alternate NHs are directed in opposite directions with respect to each other as in **2b**[6] and the two phenylene rings are inclined away from the core forming an overall distorted bowl-like structure (Figure 1). Interestingly, in receptor **3**, two alternate pyrrole units reside almost in the plane of the adjacent phenylene moieties (dihedral angles 17.2° and 18.6°) while the remaining two pyrroles adopt an almost orthogonal geometry with respect to the phenylene rings (dihedral angles 80.5° and 76.2°). This near coplanarity, owing to the fusion of benzene moieties at the calix[4]pyrrole periphery, resulted in an extended π-conjugation in **3**, associated with fluorescence enhancement compared to its constituents (Φ = 0.16, Figure 2), and this effect could also be observed upon fusion of naphthalene moieties, which resulted in large red-shifted absorption and emission bands for **4** compared to naphthalene (Stokes shifts of 117 and 142 nm for **3** and **4** respectively). The observed extended π-conjugation in both hosts is well supported by the computationally obtained electrostatic potential plots, which clearly display localization of the electron density only on the two opposite pyrrole moieties

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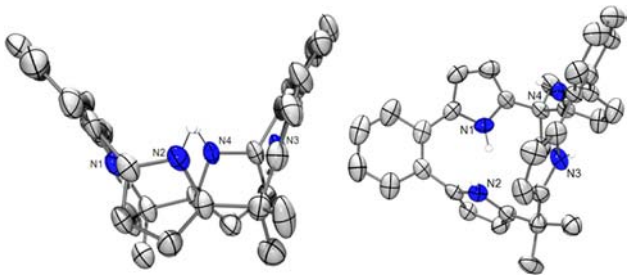
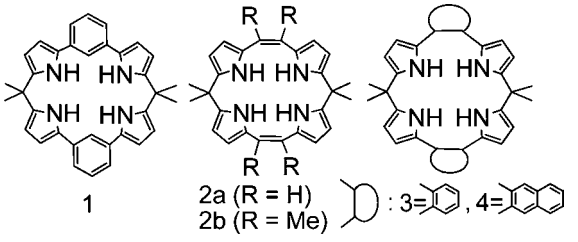


Figure 1. Two views of the solid state structure of **3**. Thermal ellipsoids are scaled to the 35% probability level. All hydrogen atoms bound to carbon atoms are omitted for clarity. Color code: blue, N; gray, C; white, H.

(blue shades around pyrrolic Ns), disposed orthogonally to the adjacent arenes (Supporting Information (SI)). To our knowledge, this type of extended conjugation had been unreported for any nonaromatic receptors including the isomer of **3** (i.e., receptor **1**).[5b] Very recently, Sessler et al. reported cyclo[*m*]pyridine[*n*]pyrroles which display extended π-conjugation only upon protonation.[11b] While these macrocycles exhibit solid state fluorescence, their host–guest chemistry is not reported.



Unlike **2a**, **3** and **4** do not exhibit any colorimetric response or appreciable change in their absorption spectra upon anion addition. However, isothermal titration calorimetry (ITC) revealed only moderate binding of fluoride ions with **3** and **4** having K_a values on the order of 10^4 (SI). This also indicates that increasing the distance between the H-bonding sites (i.e., pyrrolic NHs) of calix[4]pyrrole increases the selectivity toward the fluoride ion, while reducing its affinity. However, exploration of their binding behavior using fluorescence spectroscopy with tetrabutylammonium (TBA) salts of various anions, viz. F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, HSO_4^-, ClO_4^-, CH_3COO^-, NO_3^-, CN^-, and PF_6^-, in acetonitrile revealed interesting results. For example, the initial screening showed that only the fluoride ion exhibits a strong interaction with the receptors, whereas acetate interacts to a lesser degree (Figure 3). Further, upon addition of these two anions, **3** displays fluorescence enhancement (*turn-on*), hitherto not observed for this class of macrocycles, accompanied by a bathochromic shift (26 nm), whereas that led to only a decrease in fluorescence intensity (*turn-off*) in the case of **4**

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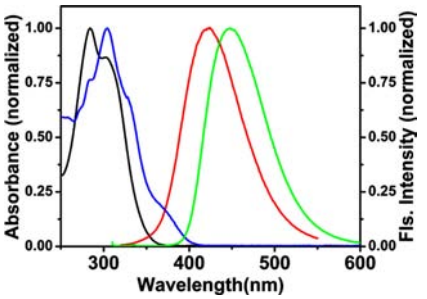

Figure 2. Absorption spectra of **3** (black) and **4** (blue) and corresponding emission spectra (red and green) in CH_3CN. λ_{ex} = 292 nm for **3** (1.06×10^{-6} M) and 304 nm for **4** (2.01×10^{-6} M).

(Figure 3). The former exhibits higher sensitivity than the latter, with a detection limit of 80 and 300 nM for the fluoride ion respectively (SI).[13] These observations were well supported by time-resolved fluorescence decay measurements. The singlet-state lifetime of receptor **3** was 0.68 ns in the unbound state, which dramatically increases to 5.68 ns upon fluoride ion binding. Yet, the singlet-state lifetime of receptor **4** (5.38 ns) remains unchanged even in the presence of a higher fluoride ion concentration (SI).

As our attempts to obtain diffraction quality crystals so far remain futile, to gain insight into the host–guest interactions, we performed density functional theory (DFT) calculations. The optimized structures reveal the approach of anions from the concave side of the bowl-like structure attained by the host upon complexation, to facilitate anion–π interactions (Figure 4). Complexation of anion led to the routine conformational change from the 1,3-alternate to the cone conformation of the four pyrrole units to bind the fluoride ion through N–H...F H-bonds. However, closer inspection revealed that the cone is no longer a regular one as observed for simple calix[4]pyrrole systems.[1a,5b,12] Here two pyrrole moieties of one dipyrromethane unit are in a relatively more planar conformation with the arenes (dihedral angles 41.76°, 41.77° for **3**, and

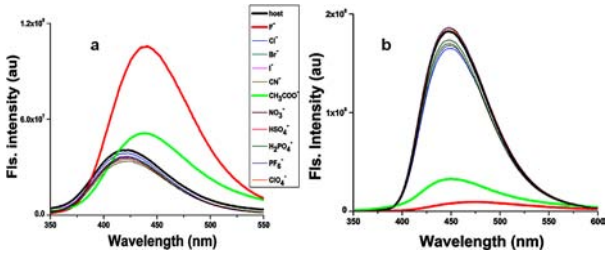

Figure 3. Fluorescence spectra of (a) **3** (1.06×10^{-6} M) and (b) **4** (2.01×10^{-6} M) upon addition of various anions (as their tetrabutylammonium salts) in CH_3CN. λ_{ex} = 292 nm for **3** and 304 nm for **4**.

42.51°, 42.40° for **4**) than the remaining two pyrroles (dihedral angles 80.18°, 80.29° for **3**, and 79.00°, 79.61° for **4**) of the other dipyrromethane moiety (SI). This again confirms, albeit qualitatively, that the extended conjugation observed in the calix[4]pyrrole derivatives still persists even upon complexation, particularly in the case of **3**, where otherwise the complexation should have resulted in the decrease of fluorescence, owing to the breakdown of the extended π-conjugation (in a regular cone conformation). Further, determination of HOMO and LUMO energies for the hosts and their fluoride and acetate complexes in the gas phase as well as in different solvents clearly indicate stabilization of the complexes in the presence of solvents; however as the polarity of the solvents increases, the HOMOs become relatively more stabilized compared to their corresponding LUMOs (SI). As a result, the energy difference between HOMO and LUMO increases; this is probably reflected in the lack of colorimetric response noticed upon complexation in these cases. However, the charge transfer (CT) nature of the interaction between the receptors and the fluoride ion could be confirmed by the observation of EPR signals with *g*-values of 2.0052 for both **3** and **4** confirming the formation of anion radicals (SI). The solvent dependent emission spectra further suggested the CT nature in which the emission spectra of **3** and **4** are red-shifted with increasing polarity of the media. However, a complete understanding of the solvatochromic effect requires more detailed study (SI). Few generalizations may be drawn from this study. For example, the solvent effect is more pronounced in the case of the polar aprotic solvents vs polar protic or nonpolar solvents. While macrocycle **3** displays only one broad emission band around 420 nm in acetonitrile, in other polar solvents it displays a more resolved emission pattern with maxima between 350 and 360 nm and a shoulder at a longer wavelength, which resolved into a band in more polar solvents such as DMF and DMSO. The fluorescence enhancement accompanied by a bathochromic shift of the emission bands (in particular the shoulder or the band at the lower energy) upon complexation with a fluoride ion is more noticeable in the case of acetonitrile, THF, and DMSO. Yet, macrocycle **4** displays only one broad emission band with maxima around 450 nm which is not much affected by the polarity of the solvents, and complexation with a fluoride ion only led to quenching of this fluorescence. From the above studies, we can conclude that complexation of fluoride resulted in a weak charge transfer from the anion to the macrocycles, probably owing to the less planar conformation (compared to **2a**).[6] In contrast, the distorted cone structure adopted by the host–anion complexes helps them in retaining the extended π-conjugation between the alternate pyrroles and the fused arenes of the receptors. Further, the resultant CT state (upon complexation) is more fluorescent in **3**•F^- and less fluorescent in the **4**•F– complex, thereby displaying a *turn-on* and *turn-off* response respectively.

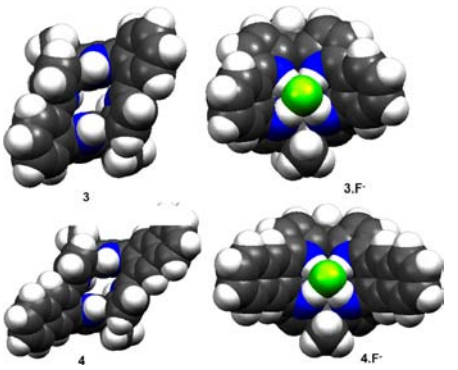

Figure 4. Space filling model of DFT-optimized structure of **3** and **4**, along with their fluoride complexes. Color code: green, F; blue, N; gray, C; white, H.

In conclusion, we have designed and synthesized two new expanded calix[4]pyrrole receptors following a new strategy: Ir-catalyzed diborylation of dipyrromethane via C–H activation, followed by '2 + 2' cyclocoupling using the Suzuki protocol. This strategy will provide a new direction for porphyrinoid synthesis in basic media in general and receptors for anions in particular. Moreover, this approach has a greater advantage over the commonly used acid catalyzed one, where the formation of a large number of products (and/or side products) occurs possibly owing to acidolysis. Both receptors exhibit fluorescence owing to extended π-conjugation with a large Stokes shift, an attribute not observed in this class of receptors. Again, the *turn-on* fluorescence observed in the case of calix[2]bispyrrolylbenzene upon binding of a fluoride and acetate ion is unprecedented in this chemistry. Presently, we are employing this new approach to develop new porphyrinoids for better host–guest selectivity.

Acknowledgment. This work is supported by D.S.T., India (Project no. SR/S1/IC-20/2007 and SR/FT/-055/2008) and C.S.I.R., India (Project no. 01(2449)/10/EMR-II). B.C., S.P.M. and N.N.P. thank C.S.I.R. for the financial support. We thank Dr. L. Giribabu, I.I.C.T., Hyderabad for help in the lifetime study. We thank S. A. M. Shamimul Ahsan, University of Hyderabad for his contribution at the initial stages, during his Master's project.

Supporting Information Available. Synthetic procedure, characterization data, and crystal data for **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.