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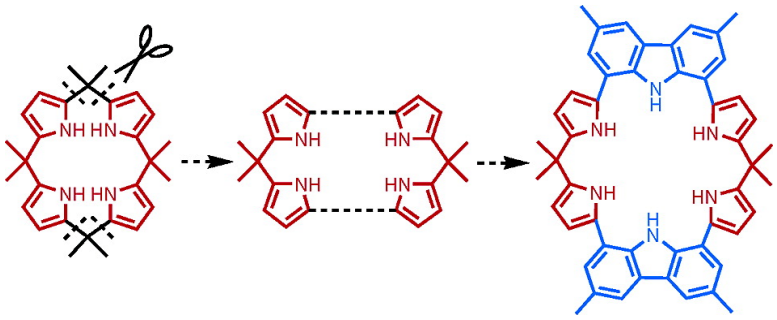

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Calix[4]pyrrole[2]carbazole: A New Kind of Expanded Calixpyrrole

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Abstract: The synthesis and anion binding properties of a new class of calixpyrrole analogue, containing two carbazole subunits in lieu of two of the four acetone bridging elements normally found in calix[4]pyrrole, is described. The compound exists in a winglike structure in the solid state, as judged from single-crystal X-ray diffraction analyses of both the free system and the corresponding benzoate anion complex. Evidence for anion binding in dichloromethane solution was obtained from static fluorescent quenching experiments; these latter revealed a slight preference for acetate relative to other carboxylate anions (e.g., benzoate, oxalate, succinate), as well as various other anionic substrates (i.e., chloride and dihydrogen phosphate). No evidence of binding was observed in the case of bromide, nitrate, and hydrogen sulfate.

Introduction

Calix[4]pyrrole, **1**, was first prepared by Baeyer in 1886.[1] However, the fact that this class of fully *meso*-substituted porphyrinogen-like macrocycle displays anion recognition properties only became appreciated in 1996 when we showed that **1** binds a fluoride anion with high affinity ($K_a > 10^5$ M^{-1}) and good selectivity in dichloromethane.[2] Subsequent efforts, devoted to improving the anion binding ability of calix[4]pyrroles and fine-tuning their inherent selectivity, have resulted in variety of structural modifications.[3] One of the most attractive of the modification strategies currently being explored involves expansion of the central calix[4]pyrrole binding cavity. This was first done by our group using a template-based approach.[4] Subsequently, the synthesis of a free-standing calix[6]pyrrole was achieved by Eichen and co-workers using a stepwise procedure that involved condensing substituted di(2-pyrrolyl)methenes with acetone.[5] Later, Kohnke and his group developed a different synthesis of expanded calix[*n*]pyrroles ($n = 5$ and 6) that relied on the oxidative opening of furan rings present in the corresponding calix[5]- or calix[6]furans and followed by reaction with ammonium acetate to effect pyrrole ring closure.[6] Our group also found that, in contrast to what is true for pyrrole itself, condensation of 3,4-difluoropyrrole with acetone leads directly to the corresponding higher order β-perfluorinated calix[*n*]pyrroles; $n = 5$, 6, and 8.[7] Recently, we introduced a different strategy for the preparation of expanded calixpyrroles that relies on the use of bipyrrole, rather than pyrrole, as the key heterocyclic building block. Using this approach we have successfully prepared several large calixpyrrole analogues, including two calix[*n*]bipyrroles ($n = 3$ and 4), a calix[2]bipyrrole[2]furan, and a calix[2]bipyrrole[2]thiophene.[8] We found that these systems act as receptors for larger anions (e.g., bromide anion, carboxylates) that are not normally bound well by simple calix[4]pyrroles. Such findings, of interest in their own right, also provide a stimulus to generate other kinds of expanded calixpyrrole analogues. In this paper we report a new approach to preparing larger calixpyrrole-type macrocycles that involves the synthetic "replacement" of two of the four acetone-derived dimethylmethylene bridging subunits with a larger heterocycle, carbazole, as illustrated in Scheme 1.

In addition to providing a convenient entry into possibly novel calixpyrrole analogues, the replacement of the bridging meth-

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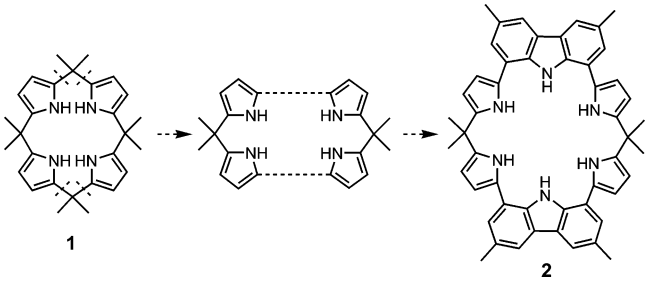
Scheme 1. Schematic Representation of the Calix[4]pyrrole Binding Cavity Expansion Strategy

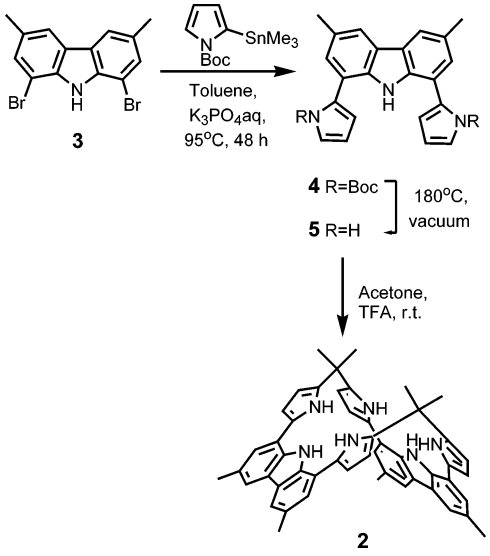


ylene groups by carbazole is attractive because it could lead to improved anion sensors. Much of the interest currently devoted to calixpyrroles reflects the fact that they may be elaborated to provide anion sensors. However, to produce such sensors it is necessary to append a reporter group, a redox active moiety[9] or a chromophore (or fluorophore),[10] to the calix[4]pyrrole binding core since the macrocycle itself does not act as an effective signaling element. By contrast, the direct incorporation of a carbazole subunit within the macrocyclic framework could provide a system that not only binds an anion but also signals its presence directly via optical means. Carbazole is a highly fluorescent molecule ($\Phi_f = 0.367$)[11] and has the further advantage in that it is easy to functionalize in the 3 and 6 positions flanking the central NH donor group.[12] As in the case of calixpyrroles, this latter moiety was considered a potential anion binding element. It displays an acidity (for NH deprotonation) that matches that of pyrrole ($pK_a = 17.1$ vs $pK_a = 17.5$)[13] but constitutes a larger and more rigid "building block". Its incorporation into a calixpyrrole-type framework was thus expected to provide a system that was "expanded" relative to **1** but which might display a very different kind of anion binding selectivity.[14,15]

Results and Discussion

The synthesis of **2** is shown in Scheme 2. Palladium-promoted coupling of 1-*tert*-butoxycarbonyl-2-(trimethylstannyl)pyrrole[16]

Scheme 2. Synthesis of Receptor **2**



to the known 1,8-dibromo-3,6-dimethyl-9*H*-carbazole[12a] (**3**) afforded compound **4**, which after deprotection gave 1,8-bis-(1*H*-pyrro-2-yl)-3,6-dimethyl-9*H*-carbazole **5**. Compound **5** was then condensed with acetone in the presence of trifluoroacetic acid, affording the target macrocycle, calix[4]pyrrole[2]carbazole (**2**), in ca. 40% yield.

Compounds **2**−**5** were characterized by standard spectroscopic techniques (cf. Supporting Information). Receptor **2** was also characterized by X-ray diffraction analysis. Diffraction-grade crystals of **2** were grown by slow diffusion of pentane into a solution of **2** in THF. X-ray diffraction analysis revealed that **2** adopts a winglike conformation (Figure 1). A molecule of *n*-pentane is located within the fold of these "wings". The dihedral angle between the two sections of **2** that make up the wings is roughly 74°, as judged by looking down the axis defined approximately by the two bridging $-C(CH_3)_2-$ *meso*-like moieties. The two carbazole NH groups point toward this axis. Two of the four pyrrole NH subunits also point in toward

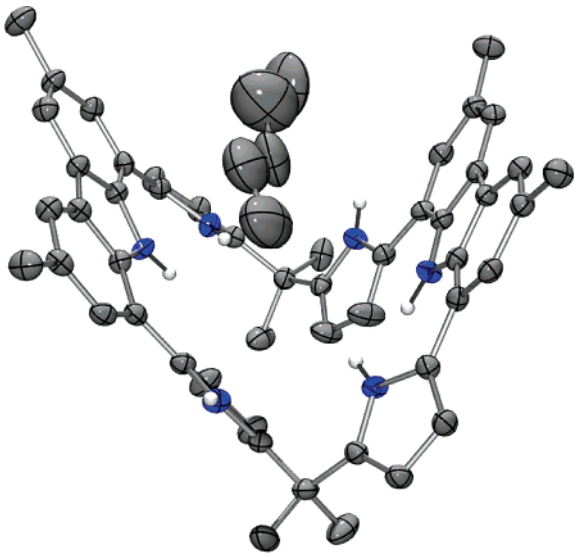


Figure 1. ORTEP-POVray rendered view of receptor **2**. A molecule of *n*-pentane, located within the fold of **2**, is also shown. Most hydrogen atoms have been removed for clarity. Thermal ellipsoids are scaled to the 50% probability level.

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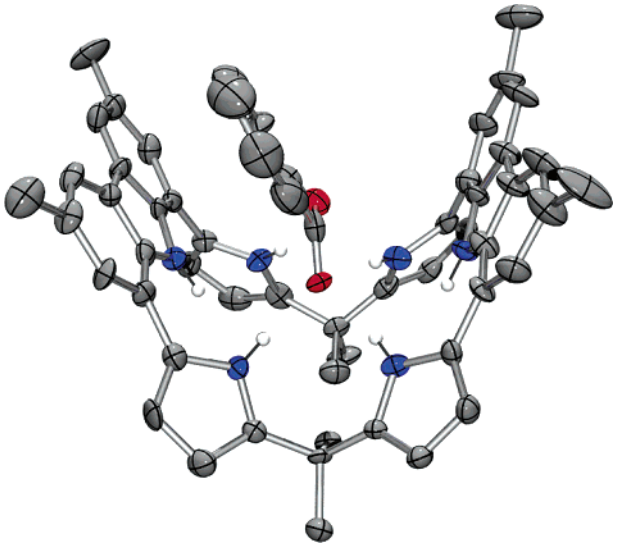

Figure 2. ORTEP-POVray rendered view of the benzoate complex of receptor **2**. The TBA countercation has been omitted for clarity. Most hydrogen atoms have been removed for clarity. Thermal ellipsoids are scaled to the 50% probability level.

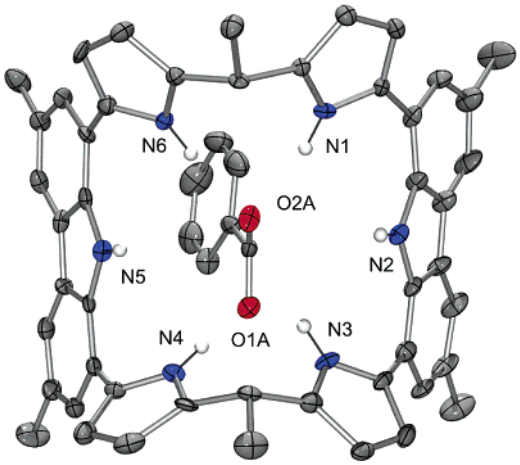

Figure 3. ORTEP−POVray rendered detailed view of the oxygen−NH interactions seen in the solid state structure of the benzoate complex of **2**. Most hydrogen atoms and two of the *meso*-methyl groups have been removed for clarity. Thermal ellipsoids are scaled to the 50% probability level.

the macrocyclic core, whereas the other two pyrrolic NH entities are found to face out from the cavity.

The structure of the 1:1 complex formed between receptor **2** and tetrabutylammonium benzoate (TBAOBz) was also solved by X-ray diffraction means (cf. Figure 2). Crystals of this complex were obtained by allowing a dichloromethane solution containing TBAOBz and **2** to undergo slow evaporation. In the solid state, the benzoate anion is found to reside deep within the "saddle" formed by the wings of macrocycle **2** fold, whereas the TBA countercation was not found to be proximate to either the macrocycle or the benzoate anion. The benzoate oxyanion is surrounded by six NH groups, with one of the oxygen atoms being close to two pyrrole NH entities and the other within hydrogen bonding distance of the other two pyrrole NH sites and, possibly, the carbazole NH-groups as well.

A detailed view of these interactions is shown in Figure 3. The O1A oxygen atom of the benzoate anion is hydrogen bonded to both N3 (2.802 Å, 132.3°) and N4 (2.788 Å, 160.8°) pyrrole nitrogen atoms. The other benzoate anion oxygen atom (O2A) is involved in hydrogen-bonding interactions to the N1 (2.872 Å, 169.1°) and N6 (2.796 Å, 176.6°) pyrrole nitrogen atoms. The distances between the two carbazole nitrogen atoms and O2A oxygen atom are 3.198 Å (N2) and 3.245 Å (N5), and nitrogen−hydrogen−oxygen angles are 108.8° and 112.2°, respectively. According to the classification proposed by Jeffrey this corresponds to a weak hydrogen bonding interaction.[17] The phenyl ring (but not the carboxylate group) of the benzoate anion is disordered, and only one orientation is shown.

One noteworthy feature of **2**, as inferred from the solid state analysis of the benzoate anion complex, is that binding in solution would be expected to take place from only one side of the saddlelike cavity. (The other side is blocked by the *meso*-methyl groups.) Thus, a 1:1 binding stoichiometry was anticipated, at least for anions of appropriate size and shape.

Initial evidence in support of anion binding in solution came from ^{1}H NMR spectroscopic titrations carried out in $CDCl_3$, a solvent chosen for reasons of solubility. Addition of various test anions, specifically acetate, benzoate, and chloride (studied in the form of their tetrabutylammonium (TBA) salts), led to a broadening of first the pyrrolic N*H* and then, at higher anion concentrations, the carbazole N*H* signals. As a general rule, these signals become broadened beyond recognition upon the addition of less than 0.3 molar equiv before reappearing after the addition of a substantial excess of the anion in question (e.g., 2.6 equiv in the case of chloride). Such behavior is qualitatively consistent with strong anion binding, as opposed to, for example, simple NH deprotonation. However, the broad nature of the peaks in question precluded accurate K_a determinations.[18]

In light of the above difficulties, the anion binding properties of **2** were studied using standard fluorescence titration methods.[10b] Prior to undertaking such measurements, the fluorescence spectrum of pure **2** was recorded in CH_2Cl_2 at different initial concentrations. The emission intensity was found to be linear in concentration over a range of 0.5 to 10 μM. Above 15 μM, however, a plot of emission vs concentration was found to deviate significantly from linearity. Therefore, K_a determinations were made at 1 and 10 μM in CH_2Cl_2 using fluorescence quenching methods. Standard curve fits matched well to a 1:1 binding profile and allowed for the calculation of the K_a values; these are collected in Table 1. The proposed 1:1 binding stoichiometry was supported by Job plots (cf. Supporting Information).

Inspection of the K_a values in Table 1 reveals that the affinity constants determined at 1 μM were significantly higher than those recorded at 10 μM. One possible explanation for this discrepancy could involve ion pairing (e.g., between the anion in question and the TBA^+ countercation), as might be expected in the relatively nonpolar solvent used for the study (CH_2Cl_2). To test this possibility, the tetrabutylammonium countercation was replaced by a bis(triphenylphosphoranylidine)ammonium cation (PPN^+) in the case of chloride and acetate. This latter countercation has been used to accelerate S_N2 reactions and is

(17) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997.
(18) Efforts to calculate the affinity constants using changes in the various CH signals did not provide reliable values. This failure is attributed to the fact that receptor **2** is aggregated under the conditions of the ^{1}H NMR spectroscopic experiments, as subsequently inferred from the fluorescence emission studies.

Table 1. Affinity Constants (M^{-1}) for the Interaction of **2** with Different Anions in Dichloromethane[a]

anion	0.5 μM	1 μM	10 μM
acetate[b]	229 000	200 000	77 000
acetate[c]	67 200	79 000	52 000
acetate[d]	148 000	96 000	63 500
benzoate[b]	77 000	67 000	31 000
oxalate[b]	31 000		
succinate[b]	9500		
$H_2PO_4^{-}$ [b]	72 000	68 000	26 000
$HP_2O_7^{3-}$ [b]	64 000		
chloride[b]	35 000	30 400	19 500
chloride[c]	32 400	17 500	10 800

[a] K_a values were determined from static fluorescence quenching experiments as described in the Experimental Section. The solvent was CH_2Cl_2 unless otherwise indicated. [b] Studied in the form of the corresponding tetrabutylammonium (TBA^+) salt. [c] The countercation was the bis(triphenylphosphoranylidine)ammonium cation (PPN^+). [d] Dry acetonitrile was used as the solvent.

thought to form much weaker ion pairs (i.e., be more appreciably disassociated) than the TBA^+ countercation.[19] However, such a replacement did not engender an appreciable difference in the calculated K_a values. In fact, for both acetate and chloride the K_a values seen for the TBA salts were seen to be bigger than those for the PPN salts. We thus do not believe that the disparity in the K_a values determined at 1 and 10 μM reflects ion pairing effects, at least not in a traditional sense. Consistent with this assumption was the observation that the K_a for acetate binding determined in CH_3CN was not appreciably higher than in CH_2Cl_2, as would be expected if cation−anion salt (TBA^+X^- or PPN^+X^-) dissociation, rather than solvent polarity effects, represented the major difference associated with this change in solvent.

Given these considerations, the difference between the K_a values determined at 1 and 10 μM is ascribed to residual aggregation effects present at the latter, higher concentration. To the extent this is true, further dilution of the receptor sample used to determine the K_a values would not be expected to effect appreciably the calculated affinity constants. As can be seen from Table 1, studies carried out at 0.5 μM[20] gave rise to K_a values that, for the most part, are the same within error as those recorded at 1 μM. We thus feel that the values recorded at these two lower concentrations provide a good indication of the anion affinities of receptor **2**.

Conclusion

The K_a values reported in Table 1 reveal that receptor **2** binds acetate strongly in both dichloromethane and acetonitrile solution. It displays a preference for this oxyanion relative to larger carboxylate-type anions (benzoate, succinate, and oxalate) but also binds the dihydrogenphosphate and chloride anions reasonably well. However, no evidence of binding was seen in the case of bromide, nitrate, and hydrogen sulfate. Thus, this macrocycle, endowed with its ability to both bind and signal the presence of an anion via fluorescence quenching means, could have a role to play as an anion sensor. As importantly, it highlights a new approach to the construction of calixpyrrole analogues wherein the bridging methylenes are replaced by various other, more elaborate spacer elements.

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Supporting Information Available: General methods and materials, synthetic experimental, representative Job plots, fluorescence quenching titrations, corresponding binding isotherms, and details of affinity constant determinations, as well as X-ray crystallographic information including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

JA045218Q

(19) Alunni, S.; Pero, A.; Reichenbach, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1747−1750.

(20) Unfortunately, a decrease in the signal-to-noise ratio as the concentration was decreased precluded further dilution studies.