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# The Elusive β-Unsubstituted Calix[5]pyrrole Finally Captured

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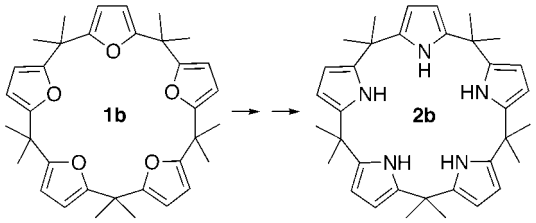
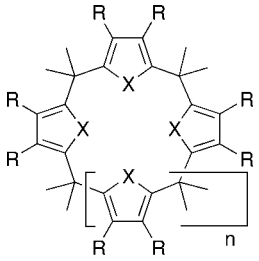
## ABSTRACT




**The *meso*-decamethyl-calix[5]pyrrole 2b was synthesized from the furan-based analogue 1b via the homologation of the furan rings to pyrrole, and its solid-state structure was determined by X-ray crystallography: surprisingly, the binding constant of 2b toward chloride is found to be lower than that of the tetrameric analogue 2a.**

After the initial discovery by Sessler[1] and his collaborators that octamethylcalix[4]pyrrole **2a** is able to complex a range of anions, including fluoride, chloride, and carboxylates as well as various neutral molecules, the chemistry of this class of compounds has become a topic of considerable and growing interest.[2] The smaller member **2a** of this family of macrocycles is readily obtainable in good yields by the acid-promoted condensation of pyrrole and acetone.[3]

The larger cyclooligomers, however, cannot be isolated as easily by this procedure: they are only present as very minor components in the reaction mixture. This failure has been ascribed to the fact that larger calixpyrroles undergo a




**1a** n = 1; R = H; X = O
**1b** n = 2; R = H; X = O
**1c** n = 3; R = H; X = O

**2a** n = 1; R = H; X = NH
**2b** n = 2; R = H; X = NH
**2c** n = 3; R = H; X = NH

**3** n = 2; R = F; X = NH

"mitosis" reaction[4] even under very mild acidic conditions to generate the tetramer **2a**. Recently, we reported the synthesis of calix[6]pyrrole **2c** by the homologation of the furan units of the analogue **1c** to pyrrole.[5] This synthesis made possible the first investigations on the host−guest chemistry of large calix[n]pyrroles with $n > 4$.[6] More

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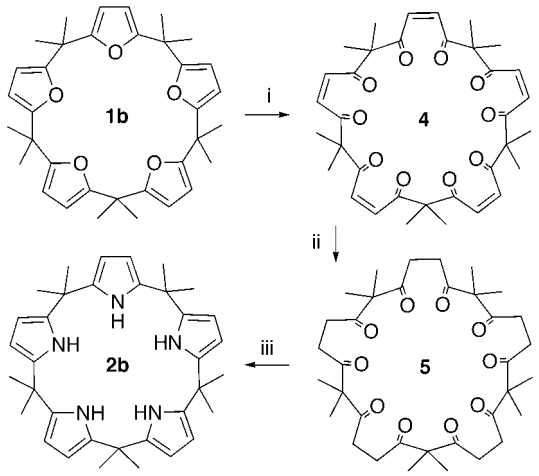
recently, Sessler and co-workers found[4a] that when the pyrrole units bear fluorine substituents at their $\beta$-positions, the mitosis reaction is a slow process. By exploiting this observation, they were able to isolate the $\beta$-fluorosubstituted calix[5]pyrrole **3** and a larger homologue containing eight pyrrole units. However, this approach still leaves the problem of obtaining the non-$\beta$-substituted parent compounds. Calix[5]pyrrole **2b** is an appealing synthetic target as it would allow its anion receptor properties to be investigated and correlated with those of its smaller and larger analogues. To date, the only known example of a $\beta$-unsubstituted calix[5]pyrrole structure is one where this macrocycle is covalently bound to a calix[5]arene.[7]

We undertook the synthesis of decamethylcalix[5]pyrrole **2b** from the known[8] calix[5]furan **1b** following the same method previously exploited[5] to obtain the calix[6]pyrrole **2c** (Scheme 1).[9] The oxidation of **1b** with MPCA in $CHCl_3$

**Scheme 1**[a]




[a] Reagents and conditions: (i) MCPA, $CHCl_3$; (ii) Zn, AcOH; (iii) $AcNH_4$, EtOH.

gave the ene-ketone **4**, which was reduced with Zn/AcOH to give the decaketone **5**. Treatment of **5** with $AcONH_4$ in refluxing ethanol led to a rapid reaction. The crude mixture, when analyzed by TLC ($SiO_2$, 7:3 hexanes/ethyl acetate), appeared to contain mainly one component, which was later characterized as the calix[5]pyrrole **2b**, together with trace quantities of a more chromatographically mobile component identified as the calix[4]pyrrole **2a**. This initially encouraging observation was, however, later severely frustrated because the larger part of the reaction mixture was found to consist of tarlike products, which are barely chromatographically mobile. Column chromatography ($SiO_2$, toluene) afforded **2b** in low but sufficient yield (ca. 1%) for a screening of its host−guest properties toward fluoride and chloride. Contrary to our expectations, we found that **2b** is sufficiently stable to allow repeated chromatographic purifications on $SiO_2$ and also to be recrystallized from boiling ethanol. No appreciable decomposition occurs in the presence of $AcONH_4$ in ethanol; thus, the low yield of the Paal−Knorr synthesis, which here is dramatically lower than that observed (42%) for calix[6]pyrrole **2c**, cannot be ascribed to a decomposition process following the initial formation of **2b**. However, the presence of trace amounts of **2a** in the crude mixture confirms that the mitosis reaction is occurring to a small extent. We believe that steric and conformational restrictions due to the smaller ring size of the "decaketone" precursor **5** of **2b**, with respect to the "dodecaketone" precursor of **2c**, may play a crucial role.

Single crystals of **2b** suitable for X-ray analysis were obtained from EtOH. The X-ray crystal structure[10] of **2b** (Figure 1) revealed the molecule to adopt a conformation

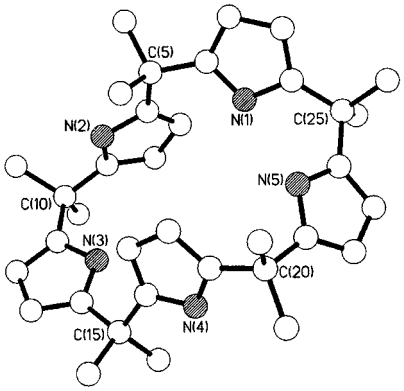



**Figure 1.** Solid-state structure of **2b** showing the alternating up/down/up/down/coplanar orientation of the pyrrole NH groups with respect to the macrocycle plane.

very similar to that of the fluorinated analogue **3**,[4a] having the pyrrole NH groups oriented in an alternating up/down/up/down/coplanar pattern with respect to the macrocycle plane. In **2b**, the five pyrrole nitrogen atoms are coplanar to within 0.39 Å (cf. 0.32 Å in **3**) and the quaternary isopropylidene carbon atoms define a five-membered ring having an envelope conformation with C(25) lying ca. 3 Å

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(9) **4**: 56%, mp 158−160 °C from EtOH; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.42 (s, 30H, $CH_3$), 6.51 (s, 10H, CH); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 21.0 ($CH_3$), 60.6 [*C*($CH_3$)$_2$], 135.0 (CH), 201.3 (CO); EI-MS *m*/*z* 621 [M + 1]$^+$. **5**: 97%, mp 130−132 °C from $CHCl_3$/EtOH; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.38 (s, 30H, $CH_3$), 2.69 (s, 10H, $CH_2$); $^{13}$C NMR $\delta$ 21.5 ($CH_3$), 32.4 ($CH_2$), 61.9 [*C*($CH_3$)$_2$], 208.3 (CO); EI-MS *m*/*z* 630 [M/+1]$^+$. **2b**: ca. 1%, mp 202−204 °C from EtOH; $^1$H NMR (300 MHz, $CD_2Cl_2$) $\delta$ 1.51 (s, 30H, $CH_3$), 5.77 (d, 10H, CH), 7.54 (bs, 5H, NH); $^{13}$C NMR $\delta$ 29.4 ($CH_3$), 35.4 ($CH_2$), 103.4(CH), 138.2 ($\beta$-C of pyrrole); EI-MS *m*/*z* 536 [M + 1]$^+$.

(10) **Crystal data for 2b:** $C_{35}H_{45}N_5$, $M$ = 535.8, monoclinic, $P2_1/c$ (no. 14), $a$ = 14.193(1) Å, $b$ = 21.277(2) Å, $c$ = 10.601(1) Å, $\beta$ = 106.96(1)°, $V$ = 3062.0(4) Å$^3$, $Z$ = 4, $D_c$ = 1.162 g/cm$^3$, $\mu$(Cu K$\alpha$) = 5.28 cm$^{-1}$, $F$(000) = 1160, $T$ = 293 K; 4540 independent measured reflections, $R_1$ = 0.044, w$R_2$ = 0.105 for 3643 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 120°$] and 382 parameters. CCDC 168706.

out of the plane of the remaining four (which are coplanar to within ca. 0.3 Å). The differences in conformation between **2b** and **3** are almost certainly a consequence of the extensive intermolecular NH···F hydrogen bonds that are present for **3** but not possible for **2b**. Clearly in both compounds the conformations must change considerably to allow the five pyrrole NH units to be directed inward to permit hydrogen-bonding interactions with an anionic guest.

For the complexation of fluoride and chloride, we expected calix[5]pyrrole **2b** to exhibit a binding constant having an intermediate value between that observed for the calix[4]-pyrrole **2a** and that estimated[11] for the calix[6]pyrrole **2c**. In fact, **2b** has the potential to form one more hydrogen bond than **2a**, and one less than **2c**. Moreover, an inspection of molecular models indicates that the size match of fluoride or chloride with the potential cavity of **2b** is considerably better than that with **2a**.[12]

The binding ability of calix[5]pyrrole **2b** toward fluoride and chloride (as their *n*-$Bu_4N^+$ salts) was evaluated by the $^1$H NMR titration method in $CD_2Cl_2$ at 22 °C following the induced shifts in the NH resonances upon complexation. The experiments were conducted by adding a concentrated solution of the salts (0.1 M) to a 0.01 M solution of the macrocycle. Consistent and reproducible results (within an average 20% error) were also obtained with more dilute solutions ($5 \times 10^{-3}$ M). Data were analyzed using the WinEQNMR fitting program.[13] When the formation of weak complexes prevented the reliable assignment of a 1:1 stoichiometry of binding from the intersection of the two tangents of the titration curves,[14] the stoichiometry was established by Job's plot experiments.[15]

When only trace amounts of water were present, the association constant $K_a$ of **2b** toward fluoride could not be determined accurately because the NH resonance, which initially occurred at $\delta$ 7.54 "disappeared" upon the first addition of salt, although it "reappeared" again at $\delta$ 12.20 when 1 equiv of salt had been added. Further additions of salt did not cause any further chemical shift changes. This latter observation is consistent with a 1:1 stoichiometry of binding. The modest $\Delta\delta$ (0.08 ppm) observed for the pyrrole $\beta$-protons is too small for a reliable determination of the $K_a$ value. When this titration was conducted in $CD_2Cl_2$ saturated with $D_2O$ (0.18% v/v), the NH pyrrole resonance remained visible throughout the titration and the $K_a$ value was found to be 14 000 ± 821 $M^{-1}$. Analogous measurements for the binding of chloride gave a $K_a$ value of 35 ± 3 $M^{-1}$. This was easily determined because the NH resonances again remained clearly visible throughout the titration experiment. The corresponding $K_a$ in wet $CD_2Cl_2$ was less than 10 $M^{-1}$. Since the values of the association constants of **2a** in wet $CD_2Cl_2$ with fluoride and chloride were not available in the literature, these were also determined and found to be 2700 ± 201 and 46 ± 8 $M^{-1}$, respectively. It is thus evident that, regardless of the presence of water, calix[4]pyrrole **2a** is a better host for chloride than calix[5]pyrrole **2b**. This finding is in sharp contrast to the expectations based on the considerations outlined above. To confirm this unexpected result, a titration experiment was performed in which equimolecular mixtures of **2a** and **2b** were titrated with *n*-$Bu_4NCl$ in wet $CD_2Cl_2$. This confirmed that in wet $CD_2Cl_2$, the $K_a$ for [**2b**·$Cl^-$] is ca. 5 times lower than that for [**2a**·$Cl^-$]. Thus, while the $K_a$ values follow the expected trend as a function of the calix size in the case of fluoride, for chloride, we are currently unable to propose an explanation for the observed results.[16]

Since the binding constant of **3** toward chloride has previously been determined[4a] in $CD_3CN$ containing 0.5% v/v $D_2O$ and found to be 41 000 ± 6000 $M^{-1}$, an analogous measurement was conducted with **2b** and the corresponding $K_a$ found to be 51 ± 11 $M^{-1}$, a value that confirms that in calixpyrroles the $\beta$-substitution with halogen atoms enhances their anion affinity. Our work demonstrates that the somewhat elusive calix[5]pyrrole **2b** can indeed be synthesized, albeit in low yield, and that it is not as unstable as originally envisaged. It has an unexpected behavior with respect to its complexation selectivity toward the halide ions relative to its larger and smaller analogues. This selectivity anomaly will form the basis of future investigations.

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**Supporting Information Available:** X-ray experimental and crystallographic data for **2b** and $^1$H NMR spectroscopic titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Binding constant of calix[6]pyrrole **2c** toward chloride in $CD_2Cl_2$ is too high to be determined by the $^1$H NMR titration method. Partition experiments with water give an estimated value of $10^4$ $M^{-1}$. This is likely to be considerably lower than that achieved in "almost anhydrous" $CD_2Cl_2$ (vide infra).

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(15) For a recent review on the determination of association constants from NMR data, see: Fielding, L. *Tetrahedron* **2000**, *56*, 6151.

(16) Low-temperature binding studies failed to provide a clue; [**2b**·$Cl^-$] remained kinetically fast on the $^1$H NMR time-scale even at −80 °C.