Synthesis and structure of nitrogen bridged calix[5]- and -[10]-pyridines and their complexation with fullerenes†

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Azacalix[5]pyridine, a heteroatom bridged calixaromatic with an odd number of arene units, and azacalix[10]pyridine, a giant molecular belt, were selectively synthesized based on a 2 + 3 macrocyclic coupling strategy; both novel macrocyclic hosts formed strong 1 : 1 complexes with fullerenes C_{60} and C_{70} in a size-selective manner with association constants up to $1.3 \times 10^5 \pm 0.03 \times 10^5$ M^{-1}.

One of the challenging and thrilling tasks in supramolecular fullerene chemistry[1] is the design and the synthesis of fullerene receptors.[2] The application of the concave–convex π–π interactions based on the complementarity principle has resulted in a few types of macrocyclic host molecules such as crown ethers,[3] γ-cyclodextrin (γ-CD),[4] cyclotriveratrylenes (CTV),[5] calix[*n*]arenes,[6] homooxacalix[3]arenes,[7] corannulenes[8] and carbon nanorings.[9] Intriguingly, polycyclic aromatic hydrocarbons[10] and porphyrins and metalloporphyrins[11] with planar π-surfaces are also able to complex fullerenes. Unfortunately, the binding of fullerenes to these synthetic receptors is weak or modest. To enhance the power of complexation with fullerenes, a strategy for the construction of molecular tweezers[2,12] has been explored.

Heteroatom-bridged calixaromatics[13] are a new generation of macrocyclic host molecules. Being different from conventional calixarenes in which the arene units are linked by methylenes, introduction of different heteroatoms into the bridging positions of calixarenes has led to a large number of novel macrocycles.[13–17] One of the noticeable features of heteroatom-bridged calixaromatics is the heteroatom-fine-tuned cavity, due to the fact that heteroatoms such as nitrogen can adopt sp^2 and/or sp^3 electronic configurations to form different degrees of conjugation with their adjacent aromatic rings. Remarkably, such fine-tuning of the cavity is self-regulated when they interact with the guest species.[15] Moreover, the tailor-made macrocyclic molecules with electron-rich and/or electron-deficient concave surfaces are readily engineered using the combination of various (hetero)aromatic rings and heteroatoms.[16] Molecular recognition studies,[15,17] though they are very limited, have already shown that heteroatom-bridged calixaromatics are unique host molecules which are able to interact with a variety of guest species.

Although a number of heteroatom-bridged calixaromatics are available,[13–17] the macrocycles containing odd numbers of aromatic rings have rarely been reported due to, most probably, the synthetic difficulty. Herein, we disclose a novel macrocyclic 2 + 3 coupling reaction which yields azacalix[5]- and azacalix[10]pyridines selectively under different conditions. As outlined in Scheme 1, 2,6-bis(methylamino)pyridine **1** reacted efficiently with two equivalents of 2,6-dibromopyridine **2** in the presence of $KOBu^t$ (3 equiv.) in refluxing THF to afford dibrominated linear trimer fragment **3** in 75% yield. The similar reaction of **1** with about one equivalent of **2** at a lower temperature gave intermediate **4** which was treated with methylamine in the presence of $CuSO_4$ at 150 °C in a sealed tube to produce diamine fragment **5** in 87% yield. The reaction between **3** and **5** was then investigated using different combinations of a catalyst, a ligand and a base in refluxing 1,4-dioxane (Table 1). No reaction was observed between **3** and **5** when CuI–DMGC or Cu_2O–salicylaldoxime was used as the catalyst (entries 1 and 2). Combination of $Pd(OAc)_2$ with 1,3-bis(diphenylphosphino)propane (dppp) did not catalyze the formation of macrocyclic compounds either (entry 3). Fortunately, the use of $Pd_2(dba)_3$ and a bidentate phosphine ligand such as dppf, dppb or dppe led to the formation of azacalix[5]pyridine **6**, albeit in low yield. Interestingly, the expanded macrocyclic homolog, azacalix[10]pyridine **7** was also isolated in a yield of 16–24% (entries 4–6). Under identical conditions, the employment of dppp as the ligand gives rise to **6** and **7** in an overall 57% yield (entry 7). The chemical yield of **6** was slightly improved to 26% when the concentration of the reactants was halved (entry 8). We then tried *N*,*N*-dimethylacetamide (DMA) instead of 1,4-dioxane as the solvent. Gratifyingly, using different reactant concentrations, azacalix[5]pyridine **6** and azacalix[10]pyridine **7** were synthesized in a selective manner in yields of 31% and 42%, respectively (entries 9 and 10).

The structures of azacalix[5]pyridine **6** and azacalix[10]pyridine **7** were established on the basis of their spectroscopic data, microanalyses and X-ray crystallography.‡ Being different from calix[5]arene, which adopts a cone conformation, azacalix[5]pyridine **6** gives a distorted 1,3-alternate conformation with one pyridine ring (B) being oriented inward (Fig. 1). While four bridging methylamino groups are almost s-*trans* to two of the adjacent pyridine nitrogen atoms N(3) and N(7), respectively, or are positioned outward, one methylamino ($H_3C(30)N(10)$) is s-*cis* to its neighboring two pyridine nitrogen atoms N(1) and N(9), or is positioned inward to the cavity of the loop. It is worth noting that careful scrutiny of the bond lengths and angles (see ESI†) of the bridging nitrogen atoms revealed that all bridging nitrogen atoms are nearly sp^2 electronically configured and form partial conjugations with both of their adjacent pyridine rings.

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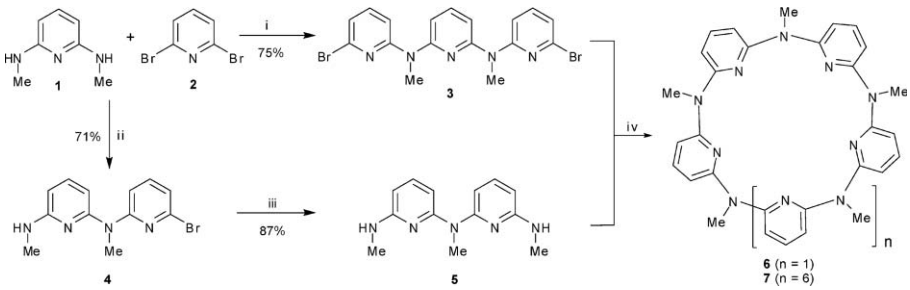
† Electronic supplementary information (ESI) available: Synthesis and characterization of **3**, **5**, **6** and **7**; absorption and emission spectra of **6** or **7** with fullerenes. See DOI: 10.1039/b705595a



Scheme 1 Synthesis of azacalix[*n*]pyridines **6** (*n* = 5) and **7** (*n* = 10). *Reagents and conditions*: (i) **1** : **2** = 1 : 2, KOBu^t (3 equiv.), THF, reflux 2 h; (ii) **1** : **2** = 1 : 0.95, KOBu^t (2 equiv.), THF, 50 °C, 1 h; (iii) $MeNH_2$–$CuSO_4$, sealed tube, 150 °C; (iv) catalyst–ligand–base, THF or DMA, 150 °C.

Table 1 Macrocyclic coupling reaction between **3** and **5**[a]

Entry	Catalyst	Ligand	Base	**6** (%)[b]	**7** (%)[b]
1	CuI	DMGC[c]	Cs_2CO_3	—	—
2	Cu_2O	Oxime[d]	Cs_2CO_3	—	—
3	$Pd(OAc)_2$	dppp	NaOBu^t	—	—
4	$Pd_2(dba)_3$	dppf	NaOBu^t	8	16
5	$Pd_2(dba)_3$	dppb	NaOBu^t	12	19
6	$Pd_2(dba)_3$	dppe	NaOBu^t	16	24
7	$Pd_2(dba)_3$	dppp	NaOBu^t	23	34
8[e]	$Pd_2(dba)_3$	dppp	NaOBu^t	26	19
9[e,f]	$Pd_2(dba)_3$	dppp	NaOBu^t	31	5
10[f,g]	$Pd_2(dba)_3$	dppp	NaOBu^t	9	42

[a] A mixture of **3** (1 mmol), **5** (1 mmol), catalyst (20%), ligand (40%) and base (3 mmol) was refluxed in 1,4-dioxane (400 mL) for 4 h. [b] Isolated yield. [c] *N*,*N*-Dimethylglycine. [d] Salicylaldoxime. [e] The concentration of the reactants was halved. [f] The reaction was carried out at 110 °C in *N*,*N*-dimethylacetamide. [g] The concentration of the reactants was increased 4-fold.

As illustrated in Fig. 2, azacalix[10]pyridine **7** adopts a parallelogram structure with C_i symmetry. The four corner pyridine rings of the parallelogram and all nitrogen atoms are located in almost the same plane with a deviation of less than 0.47 Å. The distances between N(5) and N(9) and between N(9) and N(5A) are 7.502 Å and 12.608 Å, respectively, yielding a giant molecular cavity. The bridging nitrogen atoms also adopt approximate sp^2 electronic configurations and form partial conjugations with their adjacent pyridine rings. It is also worth noting that all bridging methylamino groups are orientated outward except methyls C(12) and C(12A) are positioned inward.

Although azacalix[5]pyridine **6** and azacalix[10]pyridine **7** adopt different conformational structures in the solid state, such structures may not remain in solution. As exemplified by their NMR spectra, azacalix[*n*]pyridines **6** and **7** gave only one set of proton and carbon signals, respectively in their ^1H and ^{13}C NMR

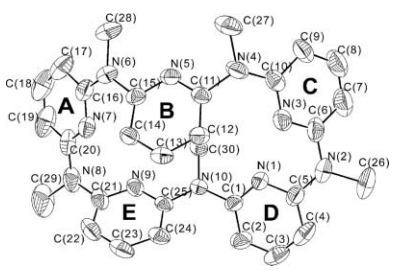


Fig. 1 Molecular structure of **6** with 50% thermal ellipsoids. (For selected bond lengths and angles, see ESI, Table S2†).

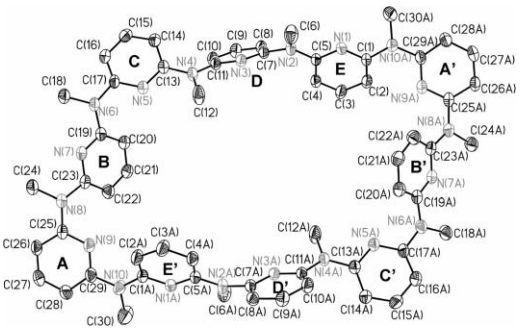


Fig. 2 Molecular structure of **7** with 50% thermal ellipsoids. The additional "A" letter in the atom labels indicates that these atoms are at $(2 - x, 1 - y, -z)$. Solvent molecules are omitted for clarity. (For selected bond lengths and angles, see ESI, Table S3†).

spectra, indicating that macrocyclic azacalix[*n*]pyridines are very fluxional, and interconversions between different conformational structures take place rapidly on the NMR time scale. The flexibility of conformational structures of azacalix[*n*]pyridines **6** and **7** may offer great advantages in the recognition of guests.

Azacalix[*n*]pyridines **6** and **7** exhibited strong affinity in complexation with fullerenes in toluene. As revealed by UV/vis titration experiments, on addition of azacalix[*n*]pyridine **6** or **7** to a solution of fullerene C_{60}, the absorption at 437.5 nm in the UV/vis spectrum increases in intensity and shifts gradually to 452.5 nm (ESI, Fig. S1 and S2†). To shed further light on the recognition of azacalix[*n*]pyridines with fullerenes, fluorescence titrations were performed (Fig. 3 and ESI, Fig. S3†). The fluorescence intensity of host molecules **6** and **7** at λ_{em} 424 nm and λ_{em} 409 nm, respectively, was quenched constantly with increasing concentration of fullerene C_{60}. The Job plot studies indicated 1 : 1 complexation of **6** and **7** with fullerene C_{60} in toluene. Based on a well-established method,[15] the fluorescence intensity F_{exp} was calibrated to F_{cal}, and calculation from the plots of F_0/F_{cal} *vs.* the concentration of fullerene C_{60} gave the association constants $2.6 \times 10^5 \pm 0.01 \times 10^5$ M^{-1} and $3.0 \times 10^5 \pm 0.008 \times 10^5$ M^{-1} for complexes C_{60}–**6** and C_{60}–**7**, respectively. By means of the same spectrophotometric measurements (ESI, Fig. S4–S7†), it was found that azacalix[*n*]-pyridines **6** and **7** showed even stronger binding ability to form 1 : 1 complexes with C_{70}, yielding the association constants $1.2 \times 10^5 \pm 0.03 \times 10^5$ M^{-1} and $1.3 \times 10^5 \pm 0.03 \times 10^5$ M^{-1}, respectively (Table 2). To the best of our knowledge, azacalix[*n*]-pyridines are among the strongest mono-macrocyclic receptors for fullerenes.[2] It is also interesting to note that the binding of

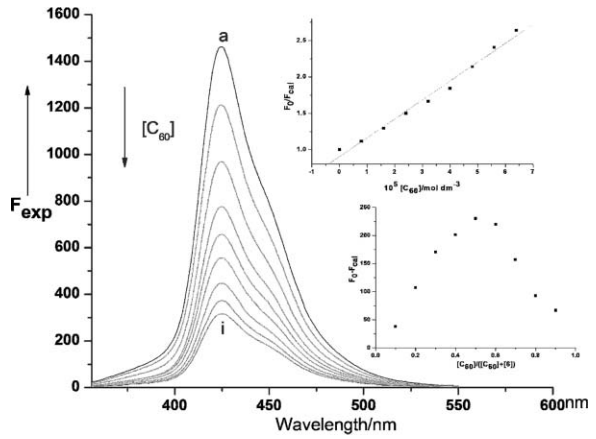


Fig. 3 Emission spectra (λ_{ex} = 336 nm) of **6** (3.2×10^{-6} mol dm^{-3}) in the presence of C_{60} in toluene at 25 °C. The concentrations of C_{60} for curves a–i (from top to bottom) are 0, 0.799, 1.60, 2.40, 3.20, 4.00, 4.80, 5.59, 6.39 ($\times 10^{-5}$ mol dm^{-3}). Insets: the top inset is the variation of fluorescence intensity F_0/F_{cal} of **6** with increasing C_{60} concentration. The bottom inset is the Job plot for **6**–C_{60} complex in toluene solution ([**6**] + [C_{60}] = 6.4×10^{-6} mol dm^{-3}).

Table 2 Association constants K_a (M^{-1}) for the 1 : 1 complexation of azacalix[*n*]pyridines with fullerenes C_{60} and C_{70}[a]

Host	Calix[4]-pyridine	Calix[5]-pyridine	Calix[8]-pyridine	Calix[10]-pyridine
C_{60}	—	$2.6 \times 10^5 \pm 0.01 \times 10^5$	$4.6 \times 10^5 \pm 0.02 \times 10^5$	$3.0 \times 10^5 \pm 0.008 \times 10^5$
C_{70}	—	$1.2 \times 10^5 \pm 0.03 \times 10^5$	$1.1 \times 10^5 \pm 0.02 \times 10^5$	$1.3 \times 10^5 \pm 0.03 \times 10^5$

[a] Calculated from plots of F_0/F_{cal} *vs.* fullerene concentration.

azacalix[*n*]pyridines with fullerenes is mainly determined by the complementarity between the host and guest (Table 2). In other words, it is the match of the sizes of host and guest that governs the binding. In the case of C_{60} complexation, for example, while small concave azacalix[4]pyridine did not interact at all, the binding ability increases in the order of azacalix[5]pyridine, azacalix[10]pyridine and azacalix[8]pyridine. To interact with the larger and oval shaped C_{70}, azacalix[10]pyridine exhibited the strongest binding, followed by azacalix[5]pyridine and azacalix[8]-pyridine. It is apparent at the current stage that azacalix[8]pyridine might provide the socket which is best fit for C_{60}, whereas azacalix[10]pyridine probably forms a cavity that complements the oval shaped C_{70}.

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Notes and references

‡ *Crystal data* **6**: $C_{30}H_{30}N_{10}$, M = 530.64, monoclinic, $P2_1/c$, a = 17.1305(11), b = 12.4187(5), c = 14.0272(2) Å, β = 113.46(3)°, V = 2737.5(2) Å^3, Z = 4, μ(Mo-Kα) = 0.082 mm^{-1}. Final residuals (361 parameters) $R1$ = 0.0823 for 4746 reflections with $I > 2\sigma(I)$, and $R1$ = 0.1131, w$R2$ = 0.1877, GoF = 1.170 for all 8747 data. CCDC 643668. **7**: $C_{66}H_{72}N_{20}O_2$, M = 1177.44, monoclinic, $P2_1/c$, a = 17.920(4), b = 8.3524(17), c = 27.638(9) Å, β = 124.47(2)°, V = 3410.4(15) Å^3, Z = 2, μ(Mo-Kα) = 0.074 mm^{-1}. Final residuals (440 parameters) $R1$ = 0.1221 for 3472 reflections with $I > 2\sigma(I)$, and $R1$ = 0.1594, w$R2$ = 0.3614, GoF = 1.295 for all 5658 data. CCDC 643669. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705595a

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