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A [2+3] fragment coupling approach to N,O-bridged calix[1]arene[4]pyridines and their complexation with C_{60}

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ABSTRACT

Functionalized N,O-bridged calix[1]arene[4]pyridines, first examples of the odd-numbered heterocalixaromatics containing mixed heteroatom bridges and mixed aromatic units, have been synthesized from the $Pd_2(dba)_3$/dppp-catalyzed 2+3 macrocyclic fragment coupling reaction between readily available staring materials. These novel macrocyclic compounds, which adopted distorted 1,3-alternate conformation in solid state, were powerful host molecules able to form 1:1 complex with fullerene C_{60} in solution, giving binding constant up to 49,494 M^{-1}.

As a new generation of macrocyclic host molecules, heterocalixaromatics have attracted a fast growing interest in recent years.[1–5] Because of the different electronic nature of heteroatoms from carbon, the heteroatom-bridged calixaromatics exhibit interesting structural and molecular recognition properties in contrast to conventional calixarenes. Due to the intrinsic nature of nitrogen that can adopt sp^2 and/or sp^3 electronic configurations to form different degrees of conjugation with its adjacent aromatic rings, the conformation and the cavity structures of the heterocalixaromatics are fine-tuned by the bond lengths and bond angles of the bridging heteroatoms. For example, by the formation of marginally different conjugations between the bridging nitrogen atoms and their neighboring pyridines, $(NMe)_4$-bridged calix[4]pyridine has been found to give cavities of different sizes to interact with the different guest species.[2d,e,l–o] In addition, the various electronic effects of the heteroatoms also influence the electron density of aromatic rings, yielding the cavity of varied electronic features. The azacalix[*n*]pyridines ($n = 5–10$),[2n] for instance, are able to interact with fullerenes C_{60} and C_{70} whereas the oxacalix[2]arene[2]triazines complex halides through anion-π interactions.[6]

Whereas the nitrogen-,[1,2] oxygen-[1,3] and sulfur-bridged[4] heterocalixaromatics with an *even* number of aromatic rings are popular, heterocalixaromatics composed of different heteroatoms and, particularly, of an *odd* number of varied aromatic rings are very rare.[2m,n] We envisioned, however, the fragment coupling approach we developed previously[1a] would enable the generation of numerous heterocalixaromatics when the combinations of varied (hetero)aromatic dinucleophilic and dielectrophilic fragments are employed. In this Letter, we report an efficient synthesis of N,O-bridged calix[1]arene[4]pyridines, the first examples of *odd-numbered calixaromatic species with two different heteroatom bridges and two different aromatic components*, from a 2+3 macrocyclic fragment coupling reaction. The method allowed the installation of the functional group on either upper rim position or on the bridging nitrogen atom. All heterocalix[5]aromatics synthesized showed excellent ability to bind fullerene C_{60}.

We initially examined the synthesis of $(NMe)_3(O)_2$-bridged calix[1]arene[4]pyridine **3** by means of macrocyclic coupling reaction between fragments **1a** and **2**. The fragment **1a** was prepared conveniently in a good yield from cheap and readily available 2,6-dibromopyridine and resorcinol (see Scheme S1, Supplementary data). In the presence of $Pd_2(dba)_3$ as a catalyst and dppp as a ligand, the reaction of **1a** with **2** produced desired 2+3 macrocyclic fragment coupling $(NMe)_3(O)_2$-bridged calix[1]arene[4]pyridine **3** as the major product. In addition, a larger macrocyclic homolog, $(NMe)_6(O)_4$-bridged calix[2]arene[8]pyridine **4**, was also isolated (Scheme 1). It is interesting to note that the total chemical yield of **3** and **4** and the ratio of **3** over **4** were dependent upon the base used. As summarized in Table 1, when Cs_2CO_3 was used as a base, products **3** and **4** were obtained in 31% and 9%, respectively (Table 1, entry 1). The use of $NaOBu^t$ lead to the increase of **4** to 23% (Table 1, entry 2). NaH appeared as a base beneficial for the selective formation of **3** (Table 1, entries 3 and 4). With NaH as the base, chemical yield of **3** was further improved to 45% when the reaction was executed in a high dilute solution (Table 1, entry 4) (see Supplementary data).

The 2+3 macrocyclic cross coupling method was successfully extended to the synthesis of functionalized N,O-bridged calix[1]arene[4]pyridines **5** and **7** starting from 3,5-dihydroxybenzoic acid methyl ester **1b** and 3,5-dihydroxybenzamide derivative

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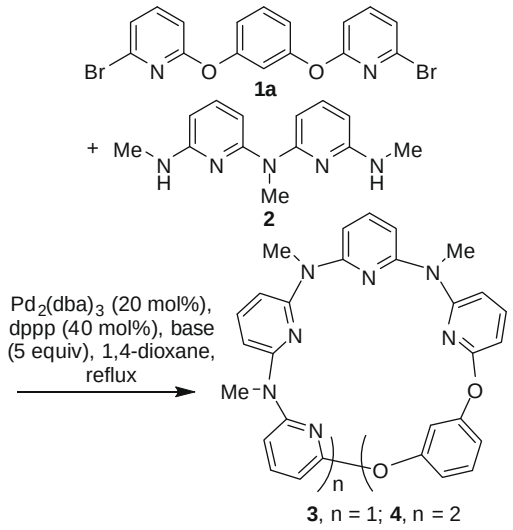


Scheme 1. Synthesis of N,O-bridged calix[*m*]arene[*n*]pyridines **3** (*m* = 1, *n* = 4) and **4** (*m* = 2, *n* = 8).

Table 1
Synthesis of N,O-bridged calix[*m*]arene[*n*]pyridines **3** and **4**

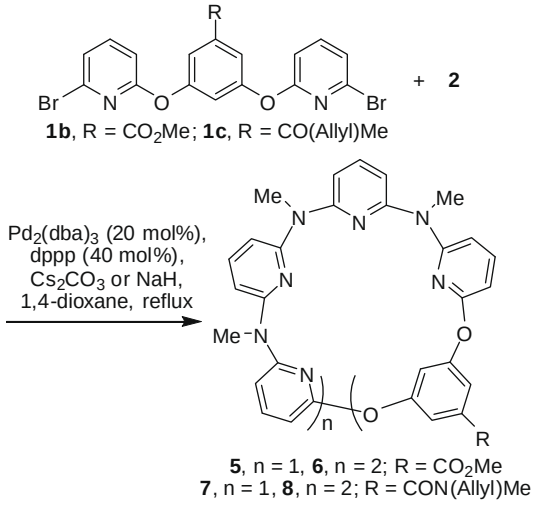
Entry	Base	Time (h)	**3**[a] (%)	**4**[a] (%)
1	Cs_2CO_3	8	31	9
2	$NaOBu^t$	5	34	23
3	NaH	30	40	15
4[b]	NaH	25	45	11

[a] Isolated chemical yield.
[b] Reaction was carried out in a high dilute solution (see Supplementary data).

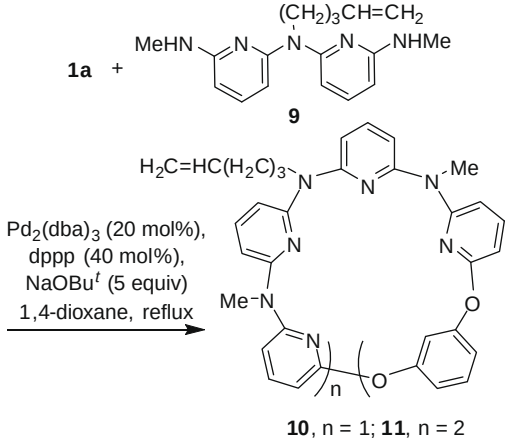
1c, respectively (Scheme S1, Supplementary data). Thus, the analogous $Pd_2(dba)_3$/dppp-catalyzed cross coupling reaction between **1b** and **2** using Cs_2CO_3 gave 28% yield of $(NMe)_3(O)_2$-bridged calix[1]arene[4]pyridine **5**, a macrocycle with ester functionality on the upper rim of benzene ring. Fragment **1c** underwent efficient macrocyclic cross coupling reaction with diamine **2** using NaH as a base to furnish amido-substituted $(NMe)_3(O)_2$-bridged calix[1]arene[4]pyridine **7** in 30% yield. In both cases, the larger macrocyclic ring homologs **6** and **8** were also obtained, respectively, in the yield of 18% and 5% (Scheme 2).

Encouraged by the efficient formation of $(NMe)_3(O)_2$-bridged calix[1]arene[4]pyridines that have a functional group on the upper rim, we then attempted the synthesis of the bridging nitrogen atom-functionalized heterocalixaromatics, a type of functionalized heterocalixaromatics that has remained largely unexplored till now.[7] As a demonstration, we chose *N*-alkenyl as a functional group because of its versatility in chemical transformations. The preparation of *N*-pent-4-enyl substituted diamine fragment **9** was carried out from *N*-alkylation of bis(6-bromopyridin-2-yl)amine followed by nucleophilic substitution reaction with methylamine in an autoclave (Scheme S2, Supplementary data). The macrocyclic cross coupling reaction between **1a** and **9** afforded desired bridging nitrogen functionalized calix[1]arene[4]pyridine product **10** in 38% yield along with calix[2]arene[8]pyridine homolog **11** in 14% yield. Changing base from NaH to $NaOBu^t$ lead to a slight improvement of the chemical yield of products, with **10** and **11** being isolated in 39% and 17%, respectively (Scheme 3).

The structure of all N,O-bridged calix[1]arene[4]pyridines synthesized was established on the basis of their spectroscopic data and microanalysis (see Supplementary data). The single crystals of **5**, **10**, and **11** grew in a mixture of dichloromethane and ethyl acetate by slow evaporation of the solvent, and their X-ray molecular structures, which were depicted in Figures 1–3, allowed unambiguous determination of the macrocyclic ring structure. In the solid state, both **5** and **10** adopted distorted 1,3-alternate conformation. The benzene ring tended to be perpendicular to the plane defined by three bridging nitrogen atoms. It is interesting to note that while each bridging nitrogen atom tended to form stronger conjugation with one of its adjacent aromatic rings, two bridging oxygen atoms formed conjugation with their neighboring pyridine rings rather than benzene ring. $(NMe)_6(O)_4$-bridged calic[2]arene[8]pyridine **11** adopted a parallelogram structure with a C_i symmetry, yielding a giant cavity. The four bridging oxygen atoms located on the same plane, and the distances between O(1) and O(2A) and between O(1) and O(2) are 17.636 Å and 4.745 Å, respectively, and angle ∠O(2)–O(1)–O(2A) is 72.86°. While two methyl groups (C(6) and C(6A)) were orientated outward of the cavity, the other two (C(22) and C(22A)) were positioned inward. Two pent-4-enyl substituents on bridging nitrogen atoms, which caused a larger *R* value (0.10) in structure refinement (Supplementary data), were located on the each side of plane. It is important to address that the solid-state conformational structures may not remain in solution. As exemplified by NMR spectra, all



Scheme 2. Synthesis of functionalized N,O-bridged calix[1]arene[4]pyridines **5** and **7**.



Scheme 3. Synthesis of bridging N-functionalized N,O-bridged calix[1]arene[4]pyridine **10**.

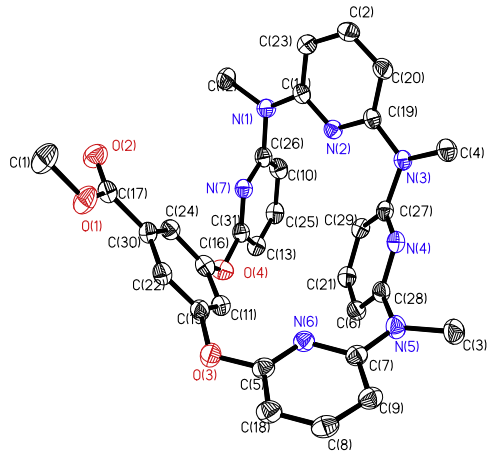


Figure 1. X-ray structure of **5** with 50% probability. Selected bond lengths: N(1)–C(14) 1.380 Å, N(1)–C(26) 1.432 Å, N(3)–C(19) 1.405 Å, N(3)–C(27) 1.415 Å, N(5)–C(7) 1.372 Å, N(5)–C(28) 1.429 Å, O(3)–C(5) 1.370 Å, O(3)–C(15) 1.394 Å, O(4)–C(16) 1.394 Å, and O(4)–C(31) 1.374 Å.

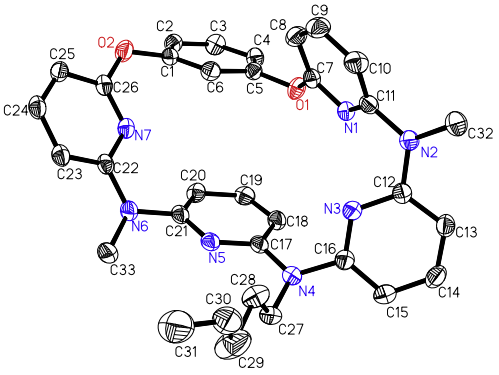


Figure 2. X-ray structure of **10** with 50% probability. Selected bond lengths: N(2)–C(11) 1.404 Å, N(2)–C(12) 1.398 Å, N(4)–C(16) 1.424 Å, N(4)–C(17) 1.392 Å, N(6)–C(21) 1.423 Å, N(6)–C(22) 1.394 Å, O(1)–C(5) 1.389 Å, O(1)–C(7) 1.379 Å, O(2)–C(1) 1.391 Å, and O(2)–C(26) 1.373 Å.

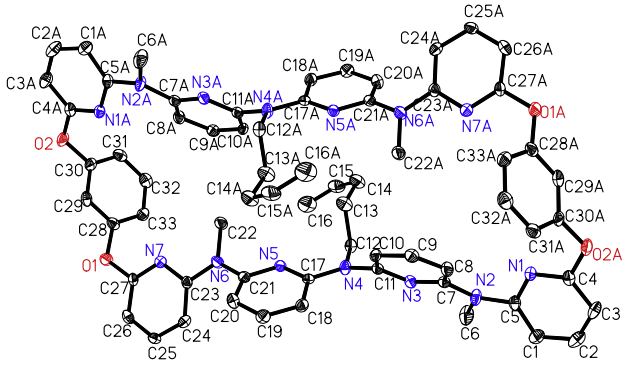


Figure 3. X-ray structure of **11** with 50% probability. Selected bond lengths: N(2)–C(5) 1.407 Å, N(2)–C(7) 1.406 Å, N(4)–C(11) 1.427 Å, N(4)–C(17) 1.389 Å, N(6)–C(21) 1.419 Å, N(6)–C(23) 1.384 Å, O(1)–C(27) 1.383 Å, O(1)–C(28) 1.399 Å, O(2)–C(30) 1.398 Å, and O(2)–C(4A) 1.381 Å.

N,O-bridged calix[1]arene[4]pyridine derivatives displayed only one set of proton and carbon signals, respectively, in their ^{1}H and ^{13}C NMR spectra, indicating that these macrocycles are very fluxional, and the interconversions between different conformational structures take place rapidly on the NMR time scale.

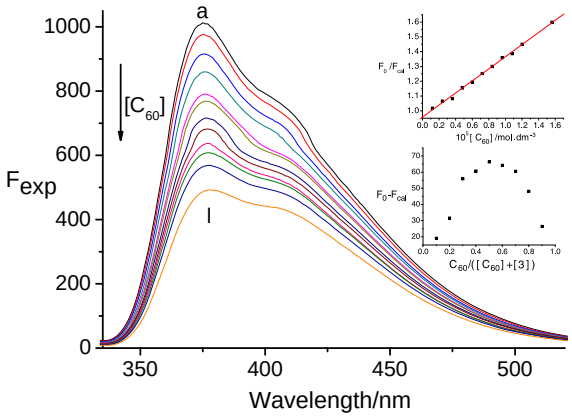


Figure 4. Emission spectra (λ_{ex} = 321 nm) of **3** (3.2×10^{-5} mol dm^{-3}) in the presence of C_{60} in toluene at 25 °C. The concentrations of C_{60} for curves a-l (from top to bottom) are 0, 1.20, 2.40, 3.60, 4.80, 6.00, 7.20, 8.40, 9.60, 10.80, 12.00, 15.60 ($\times 10^{-6}$ mol dm^{-3}). Insets: The up inset is the variation of fluorescence intensity F_0/F_{cal} of **3** with increasing C_{60} concentration. The down inset is the Job plot for **3**–C_{60} complex in toluene solution ([**3**] + [C_{60}] = 2.4×10^{-5}mol dm^{-3}).

N,O-Bridged calix[1]arene[4]pyridine compounds appeared as powerful host molecules able to interact with fullerene C_{60}. Fluorescence titration and the Job's plot experiments (Fig. 4 and Supplementary data) showed that all N,O-bridged calix[1]arene[4]pyridines synthesized formed a 1:1 complex with fullerene guest C_{60}. Based on fluorescence titration data, association constants $K_{a(1:1)}$ were calculated,[2d,8] which ranged from 35,113 ± 106 (**5**), 40,963 ± 757 (**3**), 44,342 ± 1479 (**7**), to 49,494 ± 1581 M^{-1} (**10**). The presence of an electron-withdrawing ester group on the upper rim decreased the electron density of the benzene ring, leading to the weakest binding toward C_{60}.

In summary, we have synthesized, functionalized N,O-bridged calix[1]arene[4]pyridine compounds, first examples of the odd-numbered calixaromatics with mixed heteroatom bridges and mixed aromatic components, using macrocyclic fragment coupling protocol from readily available starting materials. These novel macrocycles, which adopted distorted 1,3-alternate conformation in the solid state formed 1:1 complex with fullerene C_{60} in toluene, giving a binding constant ($K_{a(1:1)}$) up to 49,494 M^{-1}. The heterocalix[5]aromatics functionalized with an ester, amide, and alkene moiety on the upper rim position and on the bridging nitrogen would provide a unique platform for the construction of high level molecular architectures in supramolecular chemistry.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, full characterization of products, ^{1}H and ^{13}C NMR of the products, fluorescence titration results, X-ray molecular structure of **5**, **10** and **11** (CIFs)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.047.

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