

Methylazacalixpyridines: Remarkable Bridging Nitrogen-Tuned Conformations and Cavities with Unique Recognition Properties

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Abstract: Methylazacalix[*n*]pyridines (*n* = 4, 8) and methylazacalix[*m*]arene[*n*]pyridines (*m* = *n* = 2, 4) have been synthesized by a convenient fragment coupling approach starting from 2,6-dibromopyridine, 2,6-diaminopyridine, and benzene-1,3-diamine. Thanks to the intrinsic electronic nature of nitrogen, which can adopt mainly sp² hybridization, allowing it variously to conjugate, partially conjugate, or not conjugate with the adjacent one or two pyridine rings, the resulting nitrogen-bridged calixpyridine derivatives act as a unique class of macrocyclic host molecules with intriguing conformational structures offering fine-tunable cavities and versatile recognition properties.

Whilst in solution it is fluxional, in the solid state methylazacalix[4]pyridine adopts a 1,3-alternate conformation with a C_{2v} symmetry in which every two bridging nitrogen atoms conjugate with one pyridine ring. After protonation, the methylazacalix[4]pyridinium species has a different conjugation system of its four bridging nitrogen atoms, yielding the similar twisted 1,3-alternate conformations with an approximate S₄ symmetry. The cavity of

each protonated methylazacalix[4]pyridine, however, varies finely to accommodate guest species of different size and geometry, such as planar DMF or HO₂CCO₂[−] ion, a twisted HO₂CCO₂[−] ion, and a tetrahedral ClO₄[−] ion. As giant macrocyclic hosts, both methylazacalix[8]pyridine and methylazacalix[4]arene[4]pyridine interact efficiently with fullerenes C₆₀ and C₇₀ through van der Waals forces. Their ease of preparation, versatile conformational structures, and recognition properties make these multinitrogen-containing calixarenes or cyclophanes unique and powerful macrocyclic hosts in supramolecular chemistry.

Keywords: anion recognition • azacalixarenepyridines • azacalixpyridines • cavity • conformation • fullerenes

Introduction

Since Gutsche's milestone work in the 1970s,^[1] calixarene chemistry has developed to become an indispensable part of supramolecular chemistry.^[2] Whilst efforts in derivatizing the basic calixarene skeletons are proliferating,^[3] one of the more recent developments in this field is the construction of new calixarenes by replacing their phenol units with other heteroarene species, in order to tune their cavities and

therefore to alter and improve their selectivities towards recognition of various guest molecules.^[4] This has in fact resulted in a few intriguing macrocycles such as calixpyrroles,^[5] calixpyridines,^[6] and other calixheteroaromatics.^[7] In particular, calixpyrroles have been shown by Sessler^[5] to be powerful anion receptors. In contrast with these preparations of *coarsely tuned* macrocyclic molecules, construction of calixarenes with *finely tunable* cavities, through substitution of their methylene bridges with heteroatoms, has until recently remained largely unexplored^[4] because of synthetic obstacles, except in the case of tetrathiocalix[4]arenes.^[8] Nevertheless, treatment of 1,3-dichloro-4,6-dinitrobenzene with resorcinol, for example, gave a 13 % yield of a tetranitro-substituted tetraoxocalix[4]arene,^[9] whilst both the Pd^{II}-catalyzed cyclic oligomerization of 3-bromo-*N*-methylaniline^[10] and the Pd⁰-catalyzed condensation of benzene-1,3-diamine and 1,3-dibromobenzene derivatives^[11] produced mixtures of azacalix[*n*]arenes (*n* = 3–8) in very low yields. Silicon-bridged calixarenes have been synthesized by coupling of phenol or 1,3-dibromobenzene with dichlorodimeth-

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Supporting information (experimental section, optimization of the syntheses of **10**, **11**, **13**, and **14** and their ¹H/¹³C NMR and UV/Vis spectra, X-ray structure of **10**) for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

ylsilane in 16% or 12% yields, respectively,^[12] and a few heteroatom-bridged calixheteroaromatics have also been prepared by incorporating further heteroatoms into heteroaromatics.^[4] Among these, silicon-bridged calix[*n*]phospharenes are notable because they act as ligands with strong π -acceptor properties.^[13] In almost all cases, however, very low and impractical chemical yields (<20%) were obtained for heteroatom-bridged macrocyclic compounds.^[12–17]

Over a year ago we communicated an effective synthesis of azacalix[*m*]arene[*n*]pyridines ($m = n = 2, 4$) through stepwise coupling reactions between benzene-1,3-diamine and 2,6-dibromopyridine fragments.^[18] The fragment coupling strategy was later successfully applied in the efficient and practical synthesis of a number of oxygen- and/or nitrogen-bridged calix[2]arene[2]triazines.^[19] Following a similar fragment coupling approach, two Japanese groups have very recently reported the syntheses of *N*-methylazacalix[4]arene^[20] and *N*-(*p*-tolyl)azacalix[3]pyridine^[21] derivatives in moderate to good yields.

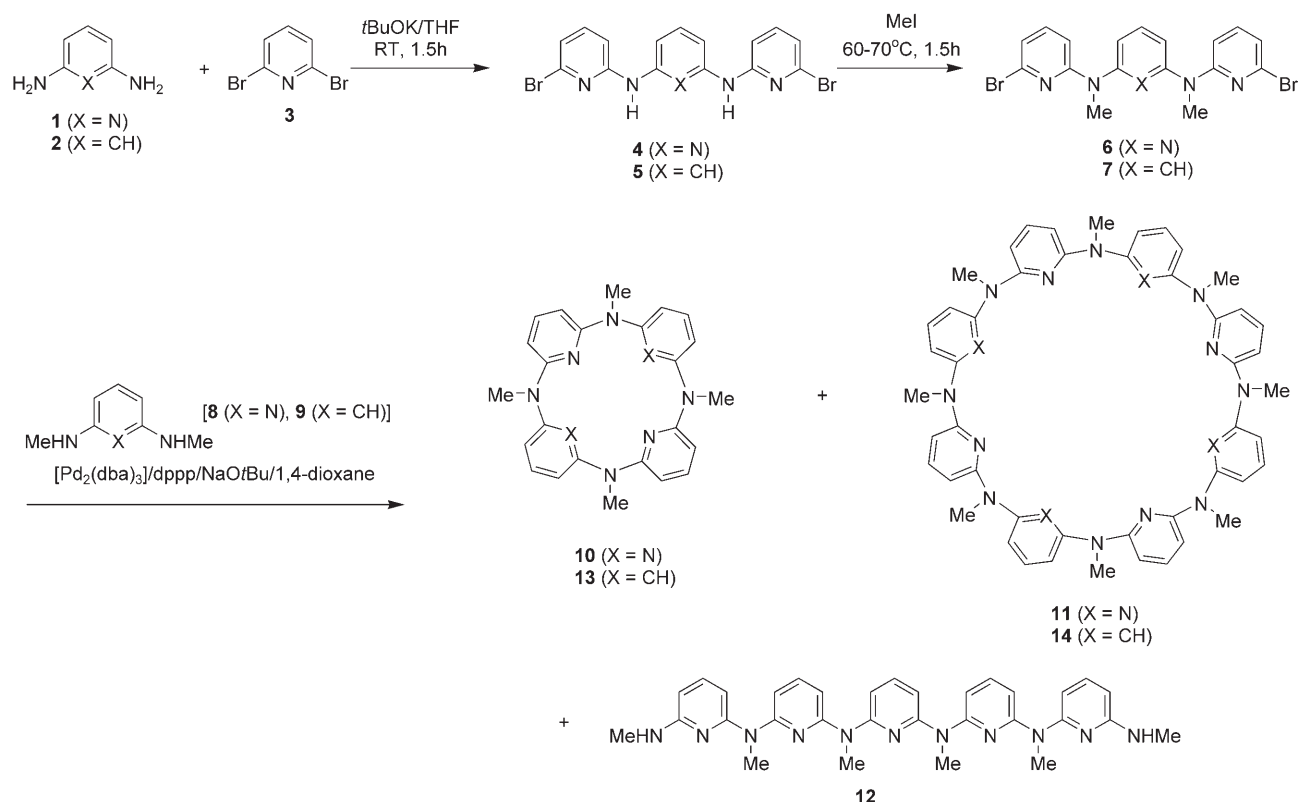
As demonstrated in our previous report,^[19] the combination of the electronic and steric effects of the bridging oxygen and nitrogen atoms regulates the cavities of 1,3-alternate conformers of aza- and/or oxa-bridged calix[2]arene[2]triazines. We envisaged that the introduction of heteroatoms, particularly amino nitrogen groups, as the bridge linkages in calixpyridines should give rise to different conformations with finely bridge-tunable macrocyclic cavities, since the bridging amino nitrogen atoms might adopt either sp^2 or sp^3 hybrid configurations, thus allowing them either to enter into or not to enter into conjugation with the neighboring pyridines. As multinitrogen-containing macrocyclic molecules, the resulting azacalixpyridines might also exhibit novel and unique recognition properties that would be subject to pH regulation. As part of our study of the supramolecular chemistry of heteroatom-bridged calixaromatics or cyclophanes, we report here a convenient fragment coupling method for the synthesis of methylazacalix[*n*]pyridines ($n = 4, 8$) and methylazacalix[*m*]arene[*n*]pyridines ($m = n = 2, 4$) and show for the first time that the bridging amino nitrogen atoms can indeed form different conjugation systems with their adjacent pyridines to provide finely tunable cavity structures in the absence and in the presence of a guest species. It is also demonstrated in detail that the larger macrocyclic host molecules methylazacalix[8]pyridine and methylazacalix[4]arene[4]pyridine are powerful spectrophotometric detection agents for the recognition of fullerenes C_{60} and C_{70} .

Results and Discussion

Synthesis: Retrosynthetically, azacalixpyridines might be synthesized by several routes: cyclic oligomerization of 2-bromo-6-(methylamino)pyridine in the presence of a palladium catalyst, for example, gave methylazacalix[6]pyridine in 8% yield, whilst a Pd^0 -catalyzed condensation between 2,6-dibromopyridine and 2,6-bis(methylamino)pyridine af-

forded a mixture of methylazacalix[4]pyridine (1.5%) and methylazacalix[6]pyridine (10%).^[17] Having considered the importance of the development of molecular diversity of macrocyclic receptors and the success of the synthesis of aza- and/or oxa-bridged calix[2]arene[2]triazines,^[19] we implemented a fragment coupling approach starting from the simple 2,6-dibromopyridine and 2,6-diaminopyridine or benzene-1,3-diamine. Condensation of 2,6-diaminopyridine (**1**) or benzene-1,3-diamine (**2**) with 2,6-dibromopyridine (**3**) in the presence of a large excess (5–10 equivalents) of a strong base such as potassium *tert*-butoxide afforded the linear trimer products **4** or **5** in good to excellent yields. The use of smaller amounts of potassium *tert*-butoxide (e.g., 2.4 equivalents) had a detrimental effect on the formation of **4** or **5**, always yielding the dimers N^2 -(6-bromopyridin-2-yl)pyridine-2,6-diamine or N^1 -(6-bromopyridin-2-yl)benzene-1,3-diamine as the major products. Further treatment of **4** or **5** with methyl iodide under basic conditions resulted in the high-yielding formation of N^2, N^6 -bis(6-bromopyridin-2-yl)- N^2, N^6 -dimethylpyridine-2,6-diamine (**6**) and N^1, N^3 -bis(6-bromopyridin-2-yl)- N^1, N^3 -dimethylbenzene-1,3-diamine (**7**) (see Supporting Information). The preparation of **6** and **7** can be facilitated in a simple one-pot operation: coupling between aromatic diamines **1** or **2** and 2,6-dibromopyridine (**3**), followed straightforwardly—without isolation and purification of **4** or **5**—by the methylation reaction with methyl iodide produced the desired **6** or **7** in yields of 84% or 78%, respectively (Scheme 1).

To synthesize methylazacalix[4]pyridine **10**, a macrocyclic coupling reaction between trimer **6** and 2,6-bis(methylamino)pyridine (**8**) by the palladium-catalyzed aryl amination procedure developed by Buchwald^[22] and Hartwig^[23] was attempted. Pd^0 -catalyzed cyclocondensation between **6** and **8** indeed proceeded smoothly to give methylazacalix[4]pyridine **10**. Interestingly, in addition to the designed 1+1 coupled product **10**, the methylazacalix[8]pyridine cyclic homologue **11** was also isolated. The formation of product **11** was interpreted as the result of the macrocyclic coupling reaction between linear trimer **6** and the pentamer intermediate **12**, which was also isolated from the reaction mixture. At this stage, however, it is hard to rule out another possible reaction pathway that comprises a double cross-coupling reaction between diamine **8** and two units of linear trimer **6** (1+2) to give a dibromo-substituted linear heptamer, followed by its macrocyclic coupling reaction with another unit of diamine **8**. To optimize the formation of azacalix[*n*]pyridine products, the reaction conditions were screened in terms of catalyst, base, substrate concentration, reactant ratio, solvent, reaction temperature, and reaction period (see Table 1 and Table 1 in the Supporting Information). It was found that the reaction outcomes were strongly dependent upon the conditions employed: to achieve an effective macrocyclic coupling reaction, the combination of $[Pd_2(dba)_3]$ (dba = *trans,trans*-dibenzylideneacetone, 1,3-bis(diphenylphosphino)propane (dppp), and NaOtBu in 1,4-dioxane at 80–102 °C appeared favorable (Scheme 1). As summarized in Table 1, a total yield of 53.1%—33.8% of methylazacalix[4]-



Scheme 1. Synthesis of calix[n]pyridines **10** ($n = 4$) and **11** ($n = 8$) and calix[m]arene[n]pyridines **13** ($m = n = 2$) and **14** ($m = n = 4$).

Table 1. Synthesis of methylazacalixpyridines **10** and **11**.^[a]

Entry	Catal. (%) ^[b]	dppp [%] ^[b]	Solvent	Temp. [°C]	Time [h]	10 [%] ^[c]	11 [%] ^[c]	12 [%] ^[c]
1	$[\text{Pd}_2(\text{dba})_3]$ (10)	20	toluene	reflux	32	20.5	18.4	13.8
2	$[\text{Pd}_2(\text{dba})_3]$ (15)	30	1,4-dioxane	reflux	2.5	33.8	19.3	11.7
3	$[\text{Pd}_2(\text{dba})_3]$ (15)	30	1,4-dioxane	80	24	16.9	20.4	8.4
4	$[\text{Pd}_2(\text{dba})_3]$ (20)	40	1,4-dioxane	reflux	2.5	35.8	15.4	4.3
5	PdCl_2 (50)	50	1,4-dioxane	reflux	24	31.5	16.0	10.6
6	$\text{Pd}(\text{OAc})_2$ (30)	30	1,4-dioxane	reflux	4.5	6.4	3.3	48.5

[a] NaOtBu (30%) was used as a base. [b] Percentage relative to reactants **6** and **8**, which were in a 1:1 ratio. [c] Yield of isolated product.

pyridine **10** and 19.3% of methylazacalix[8]pyridine **11**—was obtained in 1,4-dioxane at reflux (Table 1, entry 2). A higher catalyst loading (20%) slightly increased the chemical yield of **10** (35.8%, Table 1, entry 4), whilst a lower reaction temperature favored the formation of **11** (Table 1, entry 3). PdCl_2 , a cheaper and readily available palladium(II) catalyst, was also able to effect the macrocyclic coupling reaction, yielding **10** and **11** in acceptable yields, although a higher catalyst loading (50%) was necessary (Table 1, entry 5). Under identical conditions, however, $\text{Pd}(\text{OAc})_2$ afforded the linear pentamer **12** as the major product (Table 1, entry 6). The macrocyclic coupling reaction between linear trimer **7** and N^1,N^3 -dimethyl-benzene-1,3-diamine (**9**) proceeded equally well in boiling 1,4-dioxane, to furnish methylazacalix[m]arene[n]pyridines **13** ($m = n = 2$) and **14** ($m = n = 4$) in 21% and 22.5% yields, respectively.^[18] Again, a lower reaction temperature (80°C) gave rise

to an increased yield of **14** (39.5%), whilst a higher catalyst loading resulted in the selective formation of **13** (see Table 2 in the Supporting Information). Apart from the higher chemical yields, the fragment coupling approaches developed in our study have the advantage over other methods of constructing a

structurally diverse range of novel heteroatom-bridged calix-aromatics or cyclophanes.^[10,11,17]

Structures: Methylazacalix[n]pyridines **10** and **11** and methylazacalix[m]arene[n]pyridines **13** and **14** are crystalline products, readily giving single crystals suitable for X-ray diffraction analysis. This allowed us to study their structures in the solid state (Table 2). In contrast with the solid-state structures of azacalix[4]arene^[10a] and calix[4]pyridine^[6], methylazacalix[4]pyridine **10** has a 1,3-alternate conformation with an approximate C_{2v} symmetry (Figure 1). Several intriguing structural features of **10** can be noted:

- 1) A pair of opposite pyridine rings is almost face-to-face parallel, like a clip, with a dihedral angle of 21.9°. The N(1) and N(1A) and C(3) and C(3A) distances between the two parallel pyridines are 4.620 Å and 3.422 Å, re-

Table 2. X-ray crystallographic data for macrocyclic host molecules and their complexes.

Compound	10 -CH ₃ CN	11	10 -HClO ₄ ·DMF	10 ·2 HClO ₄	10 -HClO ₄ ·H ₂ Bi(OH)Cl ₄	10 ·2 HO ₂ CCO ₂ H·H ₂ O	13 -HClO ₄ ·CH ₂ Cl ₂	13 ·2 HI·I ₂ ·CH ₂ OH
empirical formula	C ₂₆ H ₂₇ N ₉	C ₂₄ H ₂₄ N ₈	C ₂₇ H ₃₂ ClN ₉ O ₅	C ₂₄ H ₂₆ Cl ₂ N ₈ O ₈	C ₂₄ H ₂₈ BiCl ₅ N ₈ O ₅	C ₂₈ H ₂₈ N ₈ O ₉	C ₂₇ H ₂₉ C ₁₃ N ₆ O ₄	C ₂₇ H ₃₂ I ₄ N ₆ O
<i>M_r</i>	465.57	424.51	598.07	625.43	894.77	620.58	607.91	964.19
crystal size [mm ³]	0.40 × 0.37 × 0.32	0.77 × 0.69 × 0.11	0.37 × 0.25 × 0.04	0.52 × 0.49 × 0.11	0.61 × 0.14 × 0.09	0.33 × 0.28 × 0.14	0.37 × 0.10 × 0.08	0.51 × 0.35 × 0.27
crystal system	orthorhombic	orthorhombic	triclinic	monoclinic	monoclinic	triclinic	orthorhombic	triclinic
space group	<i>Pmmn</i>	<i>Pccn</i>	<i>P</i> $\bar{1}$	<i>P2(1)/n</i>	<i>P2(1)/c</i>	<i>P1</i>	<i>Pna2(1)</i>	<i>P</i> $\bar{1}$
<i>a</i> [Å]	11.7199(7)	12.0387(5)	9.6632(4)	13.7975(6)	10.700(2)	9.5691(19)	15.774(3)	9.1832(18)
<i>b</i> [Å]	16.6292(9)	33.9080(6)	11.0917(7)	13.7100(6)	11.606(2)	11.747(2)	13.473(3)	11.184(2)
<i>c</i> [Å]	6.1808(4)	10.406(2)	14.0602(6)	14.4855(8)	26.268(5)	13.787(3)	13.507(3)	16.038(3)
α [°]	90	90	83.5930(17)	90	90	69.43(3)	90	97.71(3)
β [°]	90	90	70.534(3)	91.0020(10)	96.14(3)	82.24(3)	90	92.98(3)
γ [°]	90	90	85.995(2)	90	90	75.44(3)	90	91.33(3)
<i>V</i> [Å ³]	1204.59(12)	4247.8(9)	1411.12(12)	2739.7(2)	3243.5(11)	1402.6(5)	2870.7(10)	1629.3(6)
ρ [g cm ⁻³]	1.284	1.328	1.408	1.516	1.832	1.469	1.407	1.965
<i>Z</i>	2	8	2	4	4	2	4	2
<i>T</i> [K]	293(2)	293(2)	293(2)	293(2)	293(2)	293(2)	293(2)	293(2)
<i>R</i> ₁ , <i>wR</i> ₂	0.0506	0.0683	0.0697	0.0516	0.0392	0.0827	0.0610	0.0414
<i>I</i> > 2 σ (<i>I</i>)	0.150	0.1900	0.1987	0.0564	0.0740	0.2064	0.0659	0.1304
<i>R</i> ₁ , <i>wR</i> ₂ (all data)	0.0677	0.1028	0.0957	0.1887	0.0769	0.1708	0.2300	0.0507
quality of fit	0.1	0.2057	0.2131	0.0623	0.0967	0.2477	0.0864	0.1373
	0.9	1.018	1.044	0.830	0.980	1.006	0.742	1.063

spectively, indicating weak π - π interaction between these two nearly aligned pyridine rings. The other two pyridine rings, however, have an edge-to-edge orientation with a dihedral angle of 79.5°. The N(2)-N(2A) and C(6)-C(6A) distances are 4.853 and 9.063 Å, respectively.

- 2) All four pyridine nitrogens and the four bridging nitrogens lie nearly in a plane. The distance between the two neighboring pyridine nitrogen atoms is 3.353 Å, and repulsion between the two lone pairs of electrons on two nitrogen atoms is avoided.
- 3) Each bridging amino moiety adopts a near-planar configuration, with the sum of the three C-N-C angles being 353.1° and the offset distance of nitrogen and the C-C-C plane being 0.219 Å, indicating that these four nitrogens have each adopted an approximate sp² configuration.
- 4) The four methyl groups on the bridging amino groups can be divided into two pairs, each of which is nearly coplanar with one of the two flattened-orientated pyridines and *s-trans*-configured with respect to the pyridine nitrogens (the torsion angle of C(7)-N(3)-C(4)-N(2) is 20.8°). As a result, the lone pairs of electrons on the four bridging nitrogens conjugate with the two flattened-orientated pyridines (*C*_{ring}-N = 1.389 Å) and do not enter into conjugation with the two parallel pyridine rings (*C*_{ring}-N = 1.436 Å). In other words, the cavity of **10** in its crystal structure can be viewed as the product of a cyclic array of two isolated pyridine rings and two conjugated 2,6-bis(methylamino)pyridine [-2-N(Me)-Py-6-N(Me)-] segments arranged in a 1,3-alternate fashion.

It is also worth noting that, in the crystallographic cell (see Figure 1 in Supporting Information) molecules **10** arrange with high symmetry. The parallel array is assembled layer-by-layer, yielding two types of channels: one is the *endo* channel, or inherent channel, formed by the internal surface of **10**, while the other, the *exo* channel, is surrounded by the external surfaces of four **10** units. In each *exo* channel, one solvent molecule (acetonitrile) is included. The same sp² electronic configuration of the bridging nitrogens and the same conjugation systems were observed in the crystal structure of methylazacalix[2]arene[2]pyridine **13**, which adopts a twist 1,3-alternate conformation with two isolated benzene rings in a nearly parallel arrangement and two edge-to-edge orientated conjugated 2,6-bis(methylamino)pyridine [-2-N(Me)-Py-6-N(Me)-] segments.^[18]

While methylazacalix[4]arene[4]pyridine **14** adopts a double-ended spoon conformation with a large oval cavity,^[18] methylcalix[8]pyridine **12** gives a pleated loop with a *Ci* symmetry in the solid state. Unlike in **11**, **13**, and **14**—in which every two bridging amino nitrogens conjugate with one pyridine ring to form the conjugated 2,6-bis(methylamino)pyridine [-2-N(Me)-Py-6-N(Me)-] unit—the bridging nitrogens in **12** produce different types of conjugation: some bridging nitrogens, including N(2), N(6), N(2A), and N(6A), for example, are partially conjugated with their two adjacent pyridine rings, meaning that all N-C bond lengths are in the 1.401–1.408 Å range, whilst on the other hand, other bridging nitrogens, such as N(4), N(8), N(4A), and N(8A), each conjugate with only one of the neighboring pyridine rings, with the bond lengths ranging from 1.386 Å to 1.394 Å. No-

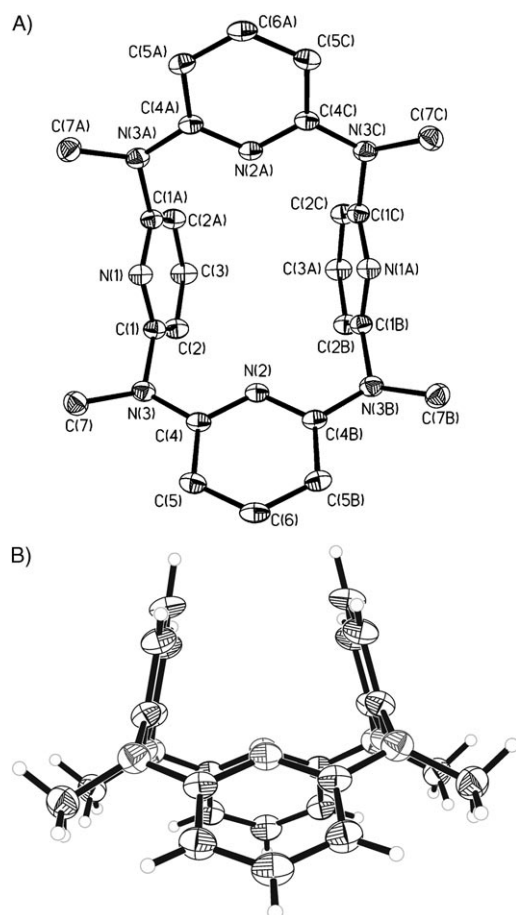


Figure 1. Crystal structure of methylazacalix[4]pyridine **10**: A) top view and B) side view. Selected bond lengths [Å]: C(1)–N(3) 1.436, C(4)–N(3) 1.389; selected interatomic distances [Å]: C(3)···C(3A) 3.422, N(1)···N(1A) 4.620, N(2)···N(2A) 4.835, C(6)···C(6A) 9.063, N(1)···N(2) 3.353.

tably, methyl groups C(24) and C(24A) on the bridging nitrogens N(8) and N(8A) are *s-cis*-configured with respect to the pyridine nitrogens N(7) and N(7A), respectively, and they are positioned towards the middle of the loop. The distance between C(24) and C(24A) is short (3.743 Å) and these two methyl groups virtually divide the cavity of the molecule into two identical parts (Figure 2).

Although in the solid state methylazacalixpyridines **10**, **11**, **13**, and **14** exist in certain conformations, with different conjugation systems of bridging nitrogens being observed, these azacalixpyridines may not be able to retain these stable conformational structures in solution. In both the ^1H and the ^{13}C NMR spectra, only one set of proton and carbon resonance signals was observed in each case. Each product, for example, gives one sharp singlet peak in the $\delta=3.17$ – 3.49 ppm range corresponding to all methyl protons, whilst the protons on all its pyridine moieties resonate at $\delta=7.37$ – 7.42 ppm and $\delta=6.36$ – 7.03 ppm as a triplet and a doublet, respectively. No signal splits were observed when the measuring temperature was decreased to -105°C , which suggests that all the calixpyridine macrocycles prepared are probably

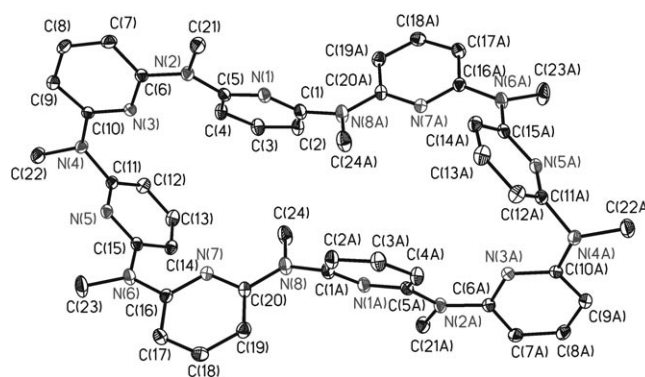


Figure 2. Crystal structure of methylazacalix[8]pyridine **11**. Top view. Selected bond lengths [Å]: C(5)–N(2) 1.408 Å, N(2)–C(6) 1.401, C(10)–N(4) 1.394, N(4)–C(11) 1.436, C(15)–N(6) 1.403, N(6)–C(16) 1.402, C(20)–N(8) 1.386, N(8A)–C(1) 1.414; selected interatomic [Å]: N(5A)···N(5) 12.777, C(13)···C(13A) 11.447, N(8)···N(8A) 4.720, C(24)···C(24A) 3.743.

very fluxional in solution, and that the rates of interconversion of various conformational structures might be very rapid relative to the NMR timescale. The high conformational mobility (relative to conventional calix[*n*]arenes derived from *p*-*tert*-butylphenol and formaldehyde) of the azacalixpyridines is most probably due to the lack of steric hindrance and the intramolecular hydrogen bonds, both being key factors in stabilizing conformational structures of calix[*n*]arenes in solution.^[2] The stability gained from the conjugation effect of the bridging nitrogen atoms with their neighboring aromatic rings seems to be insufficient to prevent the rotation of aromatic rings (both pyridine and benzene rings) around the *meta*–*meta* axes or through the annulus. Such molecular flexibility might offer great advantages in the self-regulation of the conformation and cavity through dynamic adjustment of the bridging nitrogens' electronic configurations and conjugations when they are allowed to interact with or recognize the guest species (*vide infra*).

Protonation of azacalixpyridines: As multiple-nitrogen-containing macrocyclic receptors, azacalix[*n*]pyridines were expected to exhibit binding properties towards cations. To understand the structural properties of azacalixpyridines under different environments, and also as a prelude to studying their molecular recognition properties, we first investigated the protonation of **10**, **11**, **13**, and **14** by spectrophotometric titration.

In ^1H NMR titration experiments, significant downfield shifts of almost all proton signals were observed when samples **10**, **11**, **13**, and **14** were treated with different concentrations of $\text{CF}_3\text{CO}_2\text{D}$ (Figure 3). The deshielding effect is consistent with protonation on the pyridine nitrogen atoms. In addition, in most cases, no new sets of resonance signals appeared under different acidic conditions at room temperature: in other words, in the solution phase the proton charge(s) seem(s) to be delocalized over all the pyridine nitrogen atoms. This ^1H NMR spectroscopic behavior might also indi-

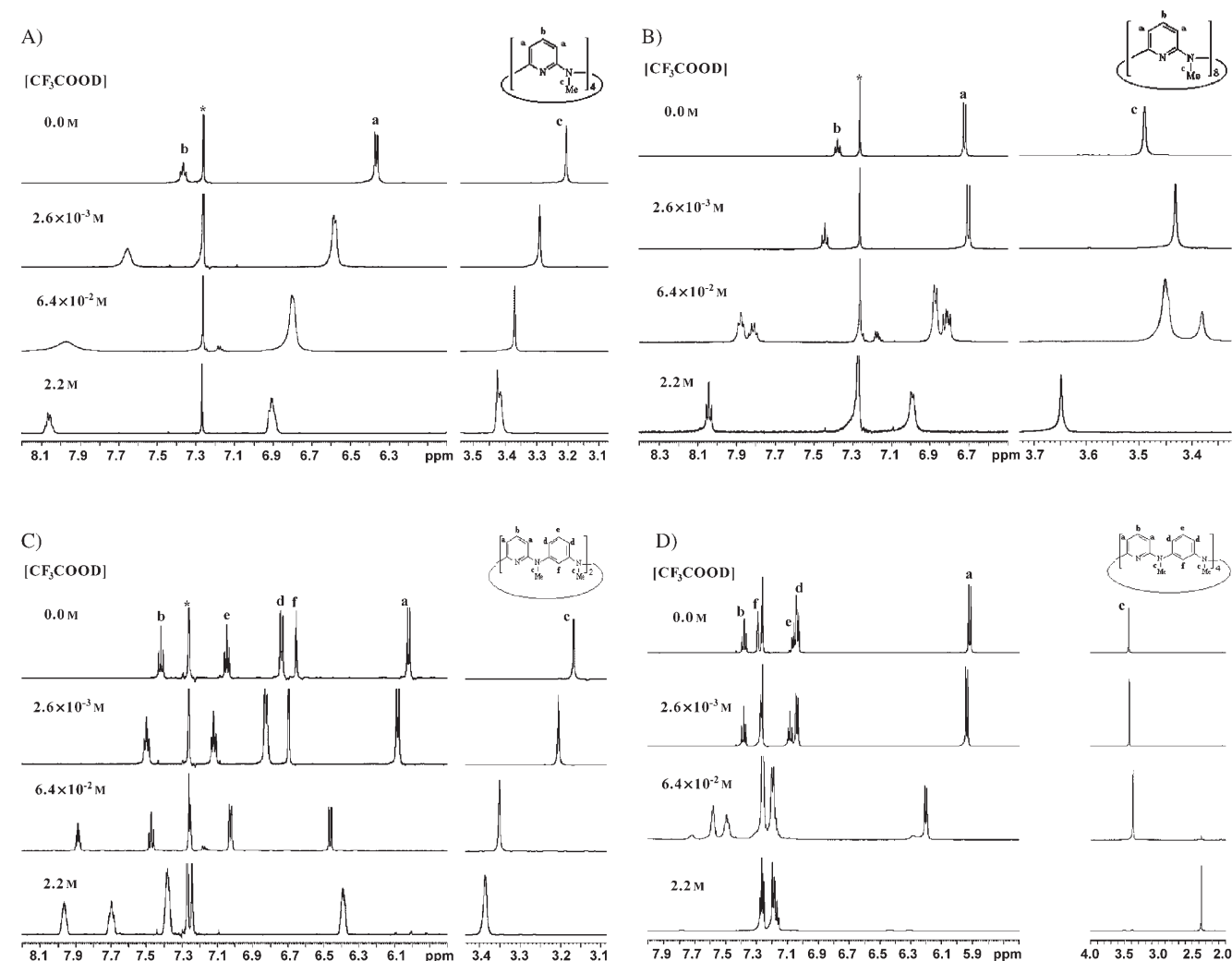


Figure 3. ^1H NMR spectra of **10** (A), **11** (B), **13** (C), and **14** (D) in CDCl_3 in the absence and in the presence of $\text{CF}_3\text{CO}_2\text{D}$ at 293 K.

cate a rapid process of proton exchanges between an unprotonated pyridine ring and a protonated one and, more importantly, very rapid interconversion of conformations of the protonated azacalixpyridine species on the NMR time-scale. It should be pointed out, however, that under one specific set of circumstances ($[\text{CF}_3\text{COOD}] = 6.4 \times 10^{-2} \text{ M}$), methylazacalix[8]pyridine **11** gave about three sets of signals (Figure 3B), whilst methylazacalix[4]pyridine **10** exhibited two sets of signals when 2.2 M of CF_3COOD were present (Figure 3A). Since the proton exchange proceeds very rapidly at room temperature, the observation of more than two sets of proton signals in these cases is most probably due to the formation of more than two relatively stable conformational structures in solution. It is also interesting to observe that in the cases of the larger macrocycles—azacalix[8]pyridine **11** and azacalix[4]arene[4]pyridine **14**—the methyl group proton signals shifted upfield under certain conditions (Figure 3B and D), which might reflect the existence of possible conformers in which the bridging methyl groups are buried in the shielding regions of aromatic rings, such as that illustrated by the crystal of **11** (see Figure 2).

To measure the protonation constants, the protonation equilibria of azacalixpyridines were also studied by UV/visible spectroscopic titrations.^[24,25] All azacalixpyridine compounds gave highly pH-dependent absorption (Figure 4; see also Figure 2 in the Supporting Information). From the UV/visible spectroscopic titration data, protonation constants ($\log K_i$ values) were obtained^[24,25] and these are listed in Table 3. The azacalixpyridine molecules display interesting protonation behavior: depending on the numbers of pyridine rings present, the azacalixpyridine macrocycles **10**, **11**, **13**, and **14** can accommodate up to four, eight, two, and four protons, respectively. The more pyridine units present within a macrocycle, the larger the $\log K_i$ value, which can be explained by considering the extensive delocalization of positive charge(s) into other pyridine nitrogens and the better minimization of the electrostatic repulsion between protonated pyridine nitrogens. Azacalix[4]pyridine **10**, with the same number of pyridine units, however, in general showed a $\log K_i$ value greater than that of azacalix[4]arene[4]pyridine **14**. This is most probably due to easier and more rapid delocalization of the charge(s) in the former macrocyclic

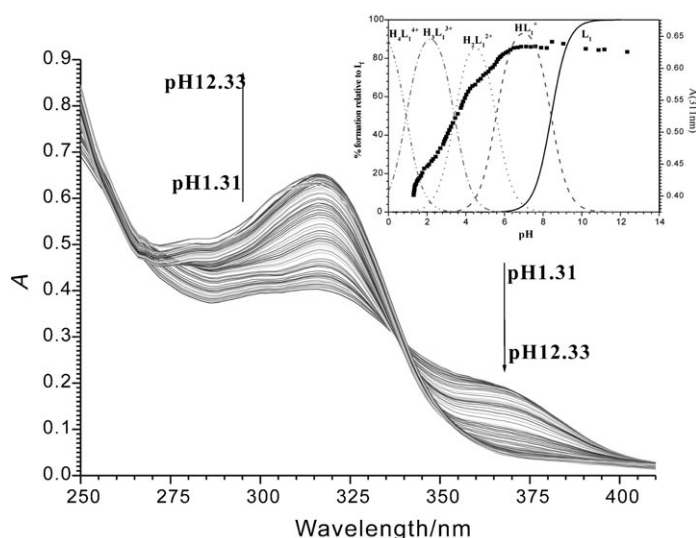


Figure 4. pH dependence of the spectra of methylazacalix[4]pyridine **10** ($[10] = 2.223 \times 10^{-5} \text{ M}$, $I = 0.1 \text{ M}$). Insert: absorption at 311 nm (black square dots) and molar fractions of the protonated forms of **10** (dashed lines).

Table 3. Logarithms of protonation constants of azacalixpyridines. ($I = 0.100 \text{ M Me}_4\text{NCl}$, $T = 20.0^\circ\text{C}$)

Reaction	log K_i			
	10	11	13	14
$L + H^+ \rightleftharpoons [HL]^+$	8.4(2)	9.9(3)	5.84(8)	7.1(7)
$[HL]^+ + H^+ \rightleftharpoons [H_2L]^{2+}$	5.5(7)	7.6(9)	1.3(0)	4.9(0)
$[H_2L]^{2+} + H^+ \rightleftharpoons [H_3L]^{3+}$	3.4(2)	6.1(1)	–	2.8(9)
$[H_3L]^{3+} + H^+ \rightleftharpoons [H_4L]^{4+}$	0.9(2)	5.0(7)	–	1.0(1)
$[H_4L]^{4+} + H^+ \rightleftharpoons [H_5L]^{5+}$	–	3.7(3)	–	–
$[H_5L]^{5+} + H^+ \rightleftharpoons [H_6L]^{6+}$	–	2.2(3)	–	–
$[H_6L]^{6+} + H^+ \rightleftharpoons [H_7L]^{7+}$	–	1.6(4)	–	–
$[H_7L]^{7+} + H^+ \rightleftharpoons [H_8L]^{8+}$	–	1.3(6)	–	–
$\Sigma \log K_i$	18.3(3)	37.7(6)	7.1(5)	15.9(8)

molecule because of the proximal arrangement of the four pyridine rings. Because of the conjugated effect and the steric hindrance, the bridging nitrogens exhibit low basicity and no further protonation on the bridging nitrogen atoms was observed in the pH range investigated.

To gain deeper insight into the interactions of azacalixpyridines with proton(s), the solid-state structures of protonated methylazacalixpyridines were studied. Fortunately, after investigating various crystallization conditions, we obtained X-ray quality crystals corresponding to the mono-, di-, and triprotonated methylazacalix[4]pyridine salts (Table 2). From the bond lengths and the intra- and intermolecular hydrogen bonds, all protonations were found to occur exclusively on the pyridine nitrogens. Notably, all protonated macrocyclic rings change their conformations from a 1,3-alternate form with C_{2v} symmetry (Figure 1) into the distorted 1,3-alternate conformation with approximate S_4 symmetry (Figure 5, Figure 6, Figure 7, and Figure 8). From the bond lengths and angles, each bridging nitrogen was judged to adopt the sp^2 hybrid configuration, conjugating with one of its adjacent pyridine rings. The cavities of protonated spe-

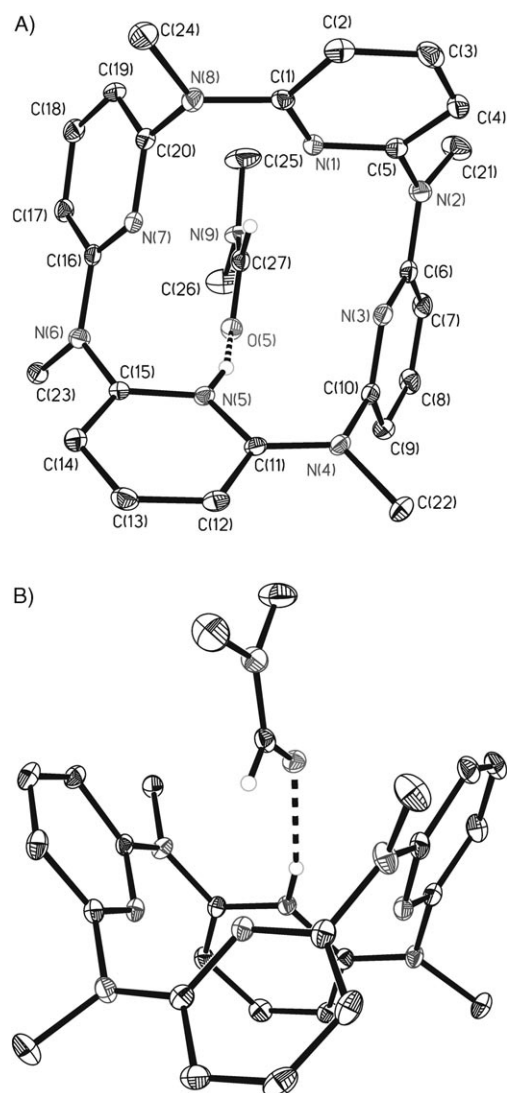


Figure 5. Molecular structure of monoprotonated methylazacalix[4]pyridine $[H10]ClO_4 \cdot DMF$: A) top view and B) side view (ClO_4^- omitted for clarity). Selected bond lengths [$\text{\AA}$]: C(5)–N(2) 1.423, N(2)–C(6) 1.375, C(10)–N(4) 1.436, N(4)–C(11) 1.346, C(15)–N(6) 1.414, N(6)–C(16) 1.393, C(20)–N(8) 1.423, N(8)–C(1) 1.381; selected interatomic distances [$\text{\AA}$]: N(1)···N(3) 3.005, N(5)···N(7) 3.012, N(5)···O(5) 2.659, C(8)···C(18) 7.345.

cies, unlike that of the parent methylazacalix[4]pyridine **10** (Figure 1), are composed of four repeating conjugated planar methylaminopyridine segments $[-6\text{-Py-2-N}(\text{CH}_3)\text{-}]$ in a distorted 1,3-alternate fashion (Figure 5 to Figure 8). All the pyridine nitrogen atoms lie nearly in a plane, while the bridging nitrogen atoms are located alternately on both sides of the plane, with four methyl groups oriented in a *trans* configuration (rtct). No intramolecular hydrogen bonding between pyridinium protons and the bridging nitrogens was observed. Instead, there are weak hydrogen bonding interactions between the protonated pyridines and the neighboring unprotonated pyridine nitrogens, as indicated by the short N–H···N distances, ranging from 2.948 to 3.060 $\text{\AA}$ (Figure 5– Figure 8), reflecting a beneficial role played by

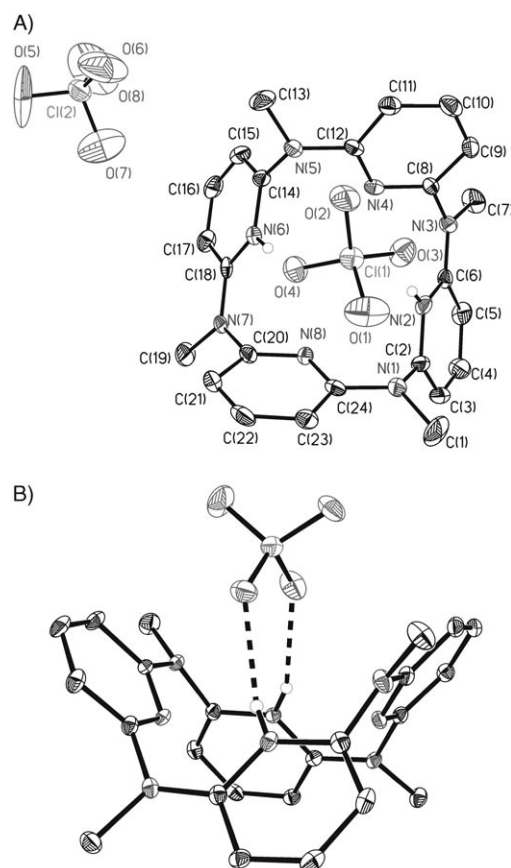


Figure 6. Molecular structure of diprotonated methylazacalix[4]pyridine $[H_2\mathbf{10}]2 ClO_4$: A) top view and B) side view (one ClO_4^- omitted for clarity). Selected bond lengths [Å]: C(6)–N(3) 1.319, N(3)–C(8) 1.427, C(12)–N(5) 1.380, N(5)–C(14) 1.397, C(18)–N(7) 1.373, N(7)–C(20) 1.418, C(24)–N(1) 1.385, N(1)–C(2) 1.395; selected interatomic distances [Å]: N(2)⋯N(4) 2.987, N(2)⋯N(8) 3.032, N(6)⋯N(4) 3.026, N(6)⋯N(8) 3.040, N(6)⋯O(4) 2.916, N(2)⋯O(3) 3.033, C(10)⋯C(22) 8.283.

the proximal pyridine rings in stabilizing the positive charge on the pyridinium unit in the distorted 1,3-alternate conformation.

Single crystals of mono- and diprotonated azacalix[2]arene[2]pyridine salts were also obtained and their solid-state structures were determined by X-ray diffraction analysis. Intriguingly, both mono- and diprotonated azacalix[2]arene[2]pyridines adopt 1,3-alternate conformations with approximate C_{2v} symmetry (Figure 9 and Figure 10), a conformation slightly different from their parent structure $\mathbf{13}^{[18]}$ but similar to that of azacalix[4]pyridine $\mathbf{10}$ in the solid state (Figure 1). Furthermore, no bridging nitrogens, which are sp^2 -configured, change their conjugation pattern in the protonated methylazacalix[4]pyridine, remaining in conjugation with the pyridine rings rather than conjugating with benzene rings. Neither stabilization effects between protonated and unprotonated pyridine rings in monoprotonated methylazacalix[2]arene[2]pyridine $\mathbf{13}$ nor repulsion between two protonated pyridines in diprotonated methylazacalix[2]arene[2]pyridine $\mathbf{13}$ were observed, the distances between two pyridine nitrogen atoms in these two salts being in the 5.080–

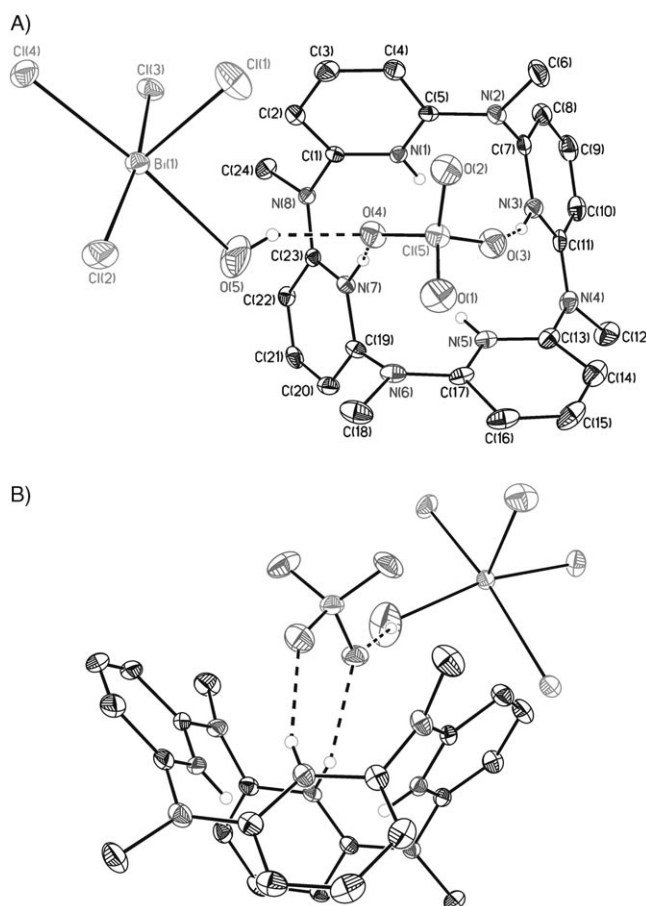


Figure 7. Molecular structure of triprotonated methylazacalix[4]pyridine $[H_3\mathbf{10}] ClO_4 \cdot OH \cdot BiCl_4$: A) top view and B) side view. Selected bond lengths [Å]: C(5)–N(2) 1.387, N(2)–C(7) 1.397, C(11)–N(4) 1.348, N(4)–C(13) 1.420, C(17)–N(6) 1.390, N(6)–C(19) 1.399, C(23)–N(8) 1.343, N(8)–C(1) 1.436; selected interatomic distances [Å]: N(1)⋯N(7) 2.955, N(1)⋯N(3) 3.063, N(3)⋯N(5) 2.964, N(3)⋯O(3) 3.086, N(7)⋯O(4) 2.965, O(4)⋯O(5) 2.875, O(5)⋯Bi(1) 2.710, C(3)⋯C(15) 8.417.

5.146 Å range. In other words, there is no interaction between the two pyridine units in the protonated methylazacalix[2]arene[2]pyridine species because of their distal locations in the macrocyclic structure.

Differently protonated methylazacalix[4]pyridine species behave like host molecular clips of different size to form sandwich-type complexes with an anion or a solvent molecule in the solid state. In the case of monoprotonated $\mathbf{10}$, for example, a DMF solvent molecule is included in the cavity through an intermolecular hydrogen bond—N(5)–H⋯O(5) (Figure 5)—whilst the diprotonated $\mathbf{10}$ forms an inclusion complex with one of the perchlorate anions through two intramolecular hydrogen bonds: N(2)–H⋯O(3) and N(6)–H⋯O(4) (Figure 6). In the presence of different guest anions, the conformationally similar triprotonated methylazacalix[4]pyridine species form varied cavities to include anions of different sizes and different geometries. As shown in Figure 7, for example, triprotonated methylazacalix[4]pyridine gives, through the formation of a pair of intermolecular bonds, a complex with a perchlorate anion that is further

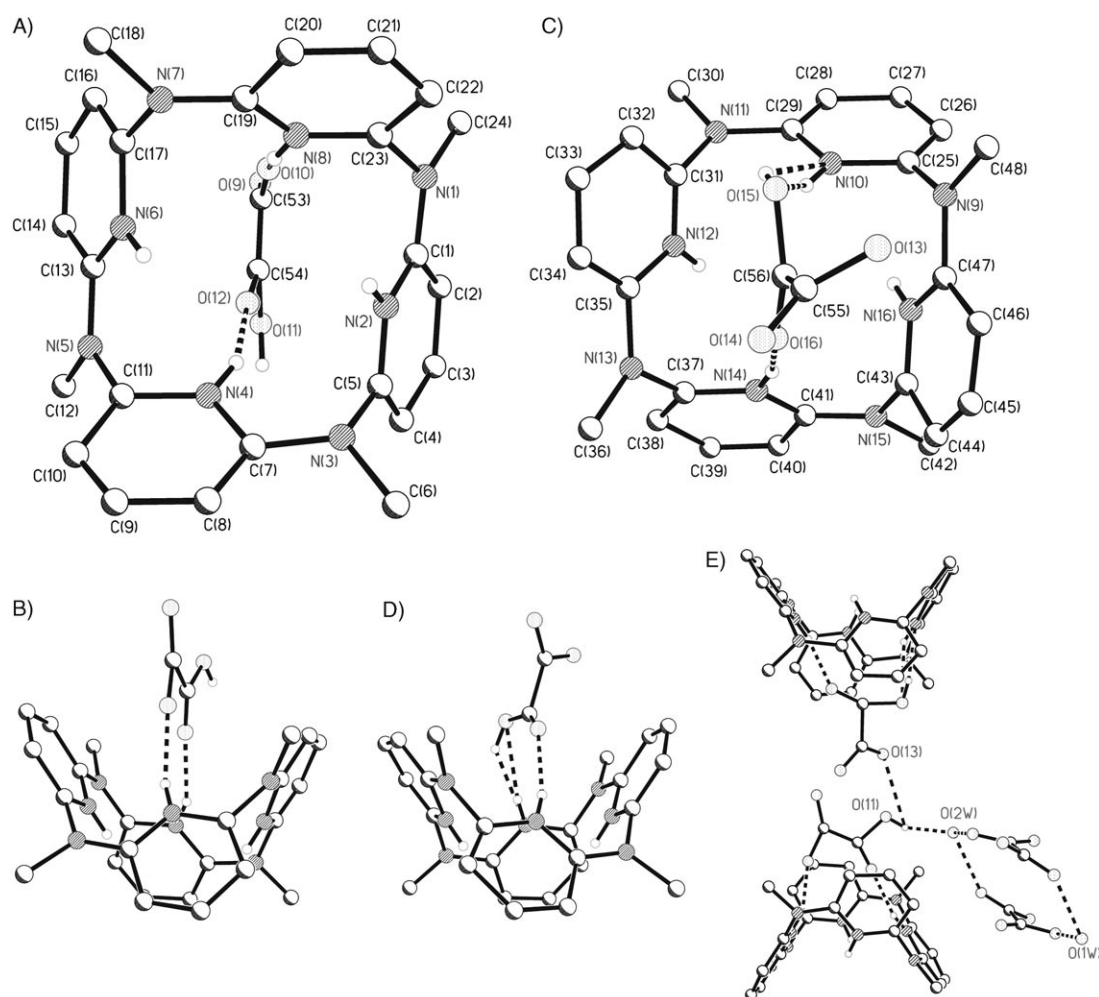


Figure 8. Molecular structure of **10**·HO₂CCO₂H·H₂O: A) top view and B) side view of the complex of the triprotonated methylazacalix[4]pyridine with a planar HO₂CCO₂[−]. C) Top view and D) side view of the triprotonated methylazacalix[4]pyridine with a twisted HO₂CCO₂[−]. E) Side view of a heterodimeric structure. Selected bond lengths [Å]: C(5)–N(3) 1.410, N(3)–C(7) 1.379, C(11)–N(5) 1.352, N(5)–C(13) 1.332, C(17)–N(7) 1.400, N(7)–C(19) 1.304, C(23)–N(1) 1.427, N(1)–C(1) 1.303, C(47)–N(9) 1.418, N(9)–C(25) 1.406, C(29)–N(11) 1.378, N(11)–C(31) 1.441, C(35)–N(13) 1.435, N(13)–C(37) 1.430, C(41)–N(15) 1.308, N(15)–C(43) 1.446; selected interatomic distances [Å]: N(4)···N(6) 2.995, N(8)···N(2) 3.050, N(8)···O(10) 2.679, N(4)···O(12) 2.704, C(3)···C(15) 7.387, N(12)···N(14) 2.997, N(16)···N(10) 2.953, N(14)···O(16) 2.734, N(10)···O(15) 2.921, C(33)···C(45) 7.413, O(11)···O(13) 2.572, O(11)···O(2W) 2.571.

hydrogen-bonded with a hydroxy moiety. It is worth noting that the embedding of a perchlorate anion in the cavity of triprotonated methylazacalix[4]pyridine is almost identical to the inclusion of a perchlorate anion in a diprotonated methylazacalix[4]pyridine (Figure 6 and Figure 7). More intriguingly, the interaction between methylazacalix[4]pyridine and oxalic acid gives two types of inclusion complexes, due to different intermolecular hydrogen bond formation. In the solid state, one of the triprotonated methylazacalix[4]pyridines forms a pair of strong intermolecular hydrogen bonds with two vicinal oxygen atoms of a planar HO₂CCO₂[−] moiety, with the N(8)–H···O(10) and N(4)–H···O(12) distances being 2.679 Å and 2.704 Å, respectively (Figure 8A and B). In the other inclusion complex, triprotonated methylazacalix[4]pyridine forms hydrogen bonds with the carboxylic group (–CO₂H) of another HO₂CCO₂[−] ion, and the N(14)–H···O(16) and N(10)···H–O(15) distances are 2.734 Å, and

2.921 Å, respectively. Notably, the included HO₂CCO₂[−] anion is heavily twisted, and the dihedral angle between the planes of –CO₂[−] and –CO₂H is around 56° (Figure 8c and d). The two discrete inclusion complexes are linked by an intermolecular hydrogen bond—O(11)–H···O(13)—giving rise to a heterodimeric structure (Figure 8e). It is also interesting to note that two other [−]O₂CCO₂[−] anions form a cyclic dimer through intermolecular hydrogen bonding with two water molecules in the crystal structure (Figure 8e).

The ability of methylazacalix[4]pyridine **10** in its different protonated forms to include guest species of different sizes and different geometries—such as a planar DMF molecule or planar HO₂CCO₂[−] ion, a heavily twisted HO₂CCO₂[−] anion, and a tetrahedral ClO₄[−] ion—is unique. This is particularly intriguing when the similar 1,3-alternate conformational structures of all the protonated macrocyclic hosts are considered. Careful scrutiny of the bond lengths between

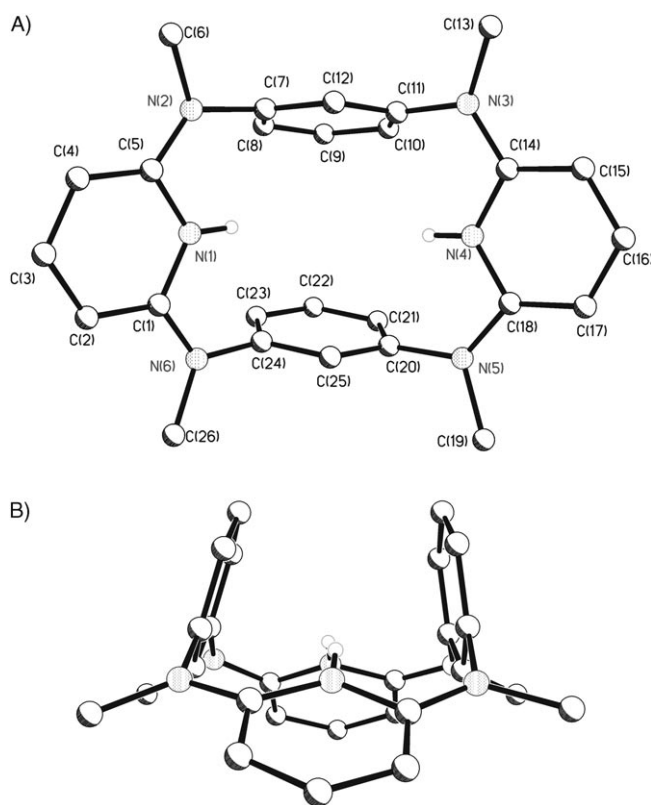


Figure 9. Molecular structure of monoprotonated methylazacalix[2]arene[2]pyridine **13**·HClO₄·CH₂Cl₂: A) top view and B) side view (ClO₄[−] and CH₂Cl₂ omitted for clarity). Proton may be located on either pyridine ring. Selected bond lengths [Å]: C(5)–N(2) 1.327, N(2)–C(7) 1.452, C(11)–N(3) 1.428, N(3)–C(14) 1.362, C(18)–N(5) 1.402, N(5)–C(20) 1.528, C(24)–N(6) 1.336, N(6)–C(1) 1.297; selected interatomic distances [Å]: N(1)···N(4) 5.080, C(3)···C(16) 9.809, C(9)···C(22) 3.510, C(12)···C(25) 4.633.

each bridging nitrogen and its adjacent aromatic carbon (see the captions for Figure 5, Figure 6, Figure 7, and Figure 8), however, allowed us to establish that the degree of conjugation of each bridging nitrogen with its neighboring pyridine varies from one protonated form to another, and differs from one bridging nitrogen to another even within a host molecule. In other words, it is the intrinsic nature of the nitrogen atom to adopt various degrees of conjugation with its adjacent aromatic ring that results in the generation of a number of fine-tuned cavities in protonated methylazacalix[4]pyridines. For example, the cavity of a protonated methylazacalix[4]pyridine species—as defined by the distance between two 4-carbon atoms of the two oppositely positioned pyridine rings on the upper rim—ranges from 7.345 Å ($d_{C(8)-C(18)}$ in [H**10**]⁺, Figure 5A), 7.387 Å ($d_{C(3)-C(15)}$ in [H₃**10**]³⁺, Figure 8A), 7.413 Å ($d_{C(33)-C(45)}$ in [H₃**10**]³⁺, Figure 8C), 8.283 Å ($d_{C(10)-C(22)}$ in [H₂**10**]²⁺, Figure 6A), to 8.417 Å ($d_{C(3)-C(15)}$ in [H₃**10**]³⁺, Figure 7A). Taking the previously discussed spectroscopic behavior of protonated methylcalix[4]pyridines into account, it is most probably the case that, through the combination of different degrees of conjugation of four bridging nitrogens with their neighboring pyridines, the highly flexible protonated methylazacalix[4]pyri-

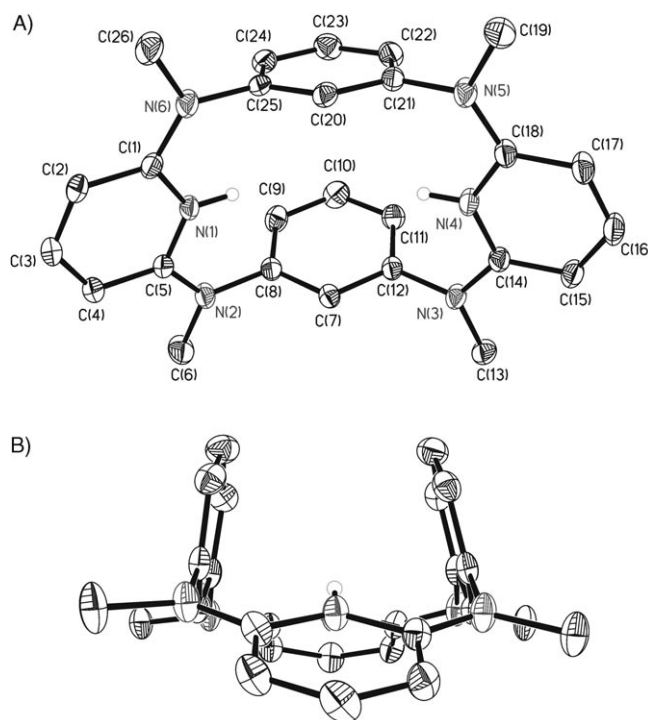


Figure 10. Molecular structure of diprotonated methylazacalix[2]arene[2]pyridine **13**·2HI·I₂·CH₃OH: A) top view and B) side view (I₃[−] and CH₃OH omitted for clarity). Selected bond lengths [Å]: C(8)–N(2) 1.423, N(2)–C(5) 1.347, C(1)–N(6) 1.336, N(6)–C(25) 1.430, C(21)–N(5) 1.435, N(5)–C(18) 1.349, C(14)–N(3) 1.353, N(3)–C(12) 1.432; selected interatomic distances [Å]: C(7)···C(20) 4.657, C(10)···C(23) 3.590, N(1)···N(4) 5.146, C(3)···C(16) 10.017.

dines are able to preorganize in solution into the most favorable conformations with tailor-made cavities to recognize different guest species during the crystallization process. It might also be speculated that the interaction—or mainly intermolecular hydrogen bonding—of an anion or a neutral molecule with a protonated methylazacalix[4]pyridine induces the latter to adopt a specific conformation through the self-adjustment of the conjugation systems of all bridging nitrogens.

Complexation with fullerenes: Much attention has been given to supramolecular fullerene chemistry because of its potential applications in chemistry, biology, and materials sciences.^[26] In the past decade, a few macrocyclic host molecules, including calix[*n*]arenes,^[26b,27] homooxalix[3]arene,^[28] cyclotrimeratrylene,^[29] β-cyclodextrin^[30] and crown ethers,^[31] and porphyrins and metalloporphyrins with planar π surfaces, have been shown to be able to interact with fullerenes.^[32] With macrocyclic host molecules **10**, **11**, **13**, and **14** to hand, we examined their recognition capabilities towards fullerene guests. The methylazacalixpyridine compounds were found to exhibit size-dependent complexation behavior with fullerenes C₆₀ and C₇₀. Neither methylazacalix[4]pyridine **10** nor methylcalix[2]arene[2]pyridine **13**, for example, is capable of forming a complex with C₆₀ or C₇₀, most probably due to the small cavities of the host molecules. In con-

trast, their larger homologues methylazacalix[8]pyridine **11** and methylazacalix[4]arene[4]pyridine **14** interact effectively with C_{60} and C_{70} molecules. Most notably, interaction between **11** or **14** and C_{60} was evidenced by a color change of a fullerene solution in toluene from its characteristic purple to light brown. As indicated by the Job plot (see Figures 4–11 in the Supporting Information), both **11** and **14** form 1:1 complexes with fullerenes C_{60} or C_{70} . The stability constants for the complexation of **11** and **14** with fullerenes C_{60} or C_{70} were calculated by fluorescence titration (Figure 11 and

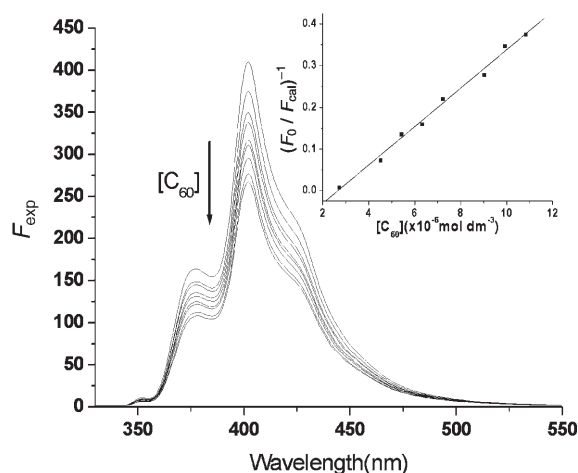


Figure 11. Emission spectra ($\lambda_{\text{exc}} = 351 \text{ nm}$) of **11** ($9.022 \times 10^{-6} \text{ mol dm}^{-3}$) in the presence of C_{60} in toluene at 25°C . The concentrations of C_{60} for curves a–k (from top to bottom) are 0.0, 2.705, 4.509, 5.410, 6.312, 7.214, 9.017, 9.919, and $10.82 \times 10^{-6} \text{ mol dm}^{-3}$. Inset: Variation of fluorescence intensity of **11** with increasing C_{60} concentration.

Figure 12), from plots of F_0/F_{cal} versus fullerene concentration^[33] and are tabulated in Table 4. The K_s values obtained for both **11** and **14** are much higher than those for calix[5]-

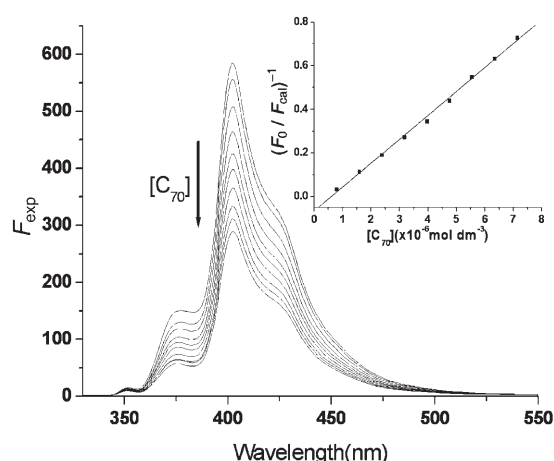


Figure 12. Emission spectra ($\lambda_{\text{exc}} = 351 \text{ nm}$) of **11** ($7.894 \times 10^{-6} \text{ mol dm}^{-3}$) in the presence of C_{70} in toluene at 25°C . The concentrations of C_{70} for curves a–j (from top to bottom) are 0.0, 0.792, 1.584, 2.376, 3.168, 3.96, 4.752, 5.544, 6.336, and $7.128 \times 10^{-6} \text{ mol dm}^{-3}$. Inset: Variation of fluorescence intensity F_0/F_{cal} of **11** with increasing C_{70} concentration.

Table 4. Stability constants K_s [M^{-1}] for the complexation of **11** and **14** with C_{60} and C_{70} .^[a]

	C_{60}	C_{70}
methylazacalix[8]pyridine 11	46050 ± 1590	109590 ± 2150
methylazacalix[4]arene[4]pyridine 14	70680 ± 2060	136620 ± 3770

[a] Calculated from plots of F_0/F_{cal} versus fullerene concentration.^[33]

and -[6]arene derivatives ($K_s = 87\text{--}2120 \text{ M}^{-1}$)^[27d,f,g] and for homooxacalix[3]arene ($K_s = (35 \pm 5) \text{ M}^{-1}$)^[27d] indicating a clear advantage of the introduction of amino groups into the bridging positions of the calixarenes. To the best of our knowledge, azacalixpyridine derivatives **11** and **14** are probably the strongest monomacrocyclic receptors to data to interact with fullerenes C_{60} and C_{70} . It is also interesting to note that azacalix[4]arene[4]pyridine **14** shows a higher affinity than azacalix[8]pyridine **11** in interaction with both C_{60} and C_{70} , and that both **11** and **14** bind more strongly with C_{70} than with C_{60} . The former can be ascribed mainly to the electronic effect, as the all-pyridine-based azacalix[8]pyridine **14** provides a less electron-rich surface than the azacalix[4]arene[4]pyridine **11**. The stronger affinities of **11** and **14** towards C_{70} than towards C_{60} are most probably attributable to steric effects: that is, to the oval-shaped giant cavities of the host molecules.

In order to understand the interactions of azacalixpyridines **11** and **14** with fullerenes at the molecular level, we attempted to determine the solid-state structures of **11**/ and **14**/fullerene complexes. Unfortunately, no crystals could be obtained. No salient changes were observed in the ^1H and ^{13}C NMR spectra of the complexes in solution. Because neither new absorption nor new emission peaks were observed in spectrophotometric titrations, the strong interaction of azacalixpyridines with fullerenes is not due to the formation of charge-transfer complexes. Although the precise reason for efficient complexation of fullerenes by azacalixpyridines still remains unclear, it is most probably explicable in terms of the van der Waals forces between sterically fitted concave and convex π surfaces. The introduction of electron-donating amino groups as the bridging units increases the electron densities of the benzene and pyridine rings, and might therefore further enhance the interactions between the curved surfaces of the macrocyclic receptors and the electron-deficient fullerenes.

Conclusion

We have developed a convenient and efficient fragment coupling approach to the synthesis of nitrogen-bridged calixpyridine macrocyclic host molecules. In the presence of excess potassium *tert*-butoxide, 2,6-diaminopyridine (**1**) and benzene-1,3-diamine (**2**) both underwent coupling reactions with 2,6-dibromopyridine (**3**) and subsequent *N*-methylation with methyl iodide in a one-pot fashion to give the corresponding linear trimers N^2,N^6 -bis(6-bromopyridin-2-yl)- N^2,N^6 -dimethylpyridine-2,6-diamine (**6**) and N^1,N^3 -bis(6-

bromopyridin-2-yl)- N^1,N^3 -dimethylbenzene-1,3-diamine (**7**) in high yields. Macrocyclic coupling reactions between the linear trimers **6** and **7** and 2,6-diaminopyridine (**1**) and benzene-1,3-diamine (**2**), catalyzed by $[\text{Pd}_2(\text{dba})_3]/\text{dppp}$ under basic conditions, proceeded smoothly and efficiently at reflux in 1,4-dioxane to afford good yields of methylazacalix[n]pyridines ($n = 4, 8$) and methylazacalix[m]arene[n]pyridines ($m = n = 2, 4$), respectively. The fragment coupling approach developed in this study should have generality in the synthesis of various nitrogen-bridged calix-(hetero)aromatics, including unsymmetric ones if different fragments are used.

The introduction of nitrogen atoms into all the bridging positions in calix[n]pyridines and in calix[m]arene[n]pyridines has resulted in a unique class of macrocyclic host molecules with intriguing conformational structures and versatile recognition properties. Thanks to their intrinsic electronic natures, the bridging nitrogens can adopt mainly sp^2 hybridization to produce conjugation, partial conjugation, and/or non-conjugation with their one and/or two adjacent pyridine rings. As a consequence, in solution these highly fluxional macrocyclic azacalixpyridine species are able to adopt specific conformations with fine-tuned cavities in order to recognize or to accommodate guest species through the formation of hydrogen bonds. For example, whilst in solution it is very fluxional, in the solid state methylazacalix[4]pyridine **10** adopts a 1,3-alternate conformation with a C_{2v} symmetry in which each pair of bridging nitrogen atoms conjugates with one pyridine ring. Through the formation of different types of conjugation between the bridging nitrogens and pyridine rings, methylazacalix[8]pyridine **11** gives a pleated loop with a C_i symmetry in the crystal structure. After protonation on the pyridine nitrogen(s), the methylazacalix[4]pyridine species changes the conjugation systems of its four bridging nitrogen atoms to yield similar twisted 1,3-alternate conformations with an approximate S_4 symmetry. The cavity of each protonated methylazacalix[4]pyridine, however, varies finely to accommodate, through the formation of hydrogen bonds, guest species of different sizes and different geometries, such as a planar DMF or $\text{HO}_2\text{CCO}_2^-$ ion, a twisted $\text{HO}_2\text{CCO}_2^-$ ion, and a tetrahedral ClO_4^- ion. To the best of our knowledge, this is probably the first example in which the cavity of a calixarene species is self-regulated by the bridging nitrogens through their conjugation systems. It has also been shown that the macrocycles synthesized undergo size-dependent interactions with fullerenes through van der Waals forces. Both methylazacalix[8]pyridine **11** and methylazacalix[4]arene[4]pyridine **14** are powerful spectrophotometric host molecules for sensing fullerenes C_{60} and C_{70} , with stability constants (K_s) as high as 46050 ± 1590 to $136620 \pm 3770 \text{ M}^{-1}$. The ease of preparation, versatile conformational structures, and potential recognition properties should make these novel multinitrogen-containing calixarenes or cyclophanes unique and powerful macrocyclic hosts in supramolecular chemistry. We are currently exploring their molecular recognition of both cations and anions and will report the results in due course.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed at the Analytical Laboratory of the Institute. All chemicals were dried or purified by standard procedures prior to use.

Preparation of N^2,N^6 -bis(6-bromopyridin-2-yl)- N^2,N^6 -dimethylpyridine-2,6-diamine (6**) and N^1,N^3 -bis(6-bromopyridin-2-yl)- N^1,N^3 -dimethylbenzene-1,3-diamine (**7**):** Under argon protection and at room temperature, a mixture of a fine powder of 2,6-diaminopyridine (**1**) or benzene-1,3-diamine (**2**) (20 mmol), 2,6-dibromopyridine (**3**) (60 mmol), and potassium *tert*-butoxide (200 mmol) was stirred vigorously for 0.5 h. Dry THF (180 mL) was added rapidly to the resulting pale yellow-brown mixture, and an exothermic reaction took place immediately, to give a dark green solution. (*Caution! Vigorous stirring is necessary. Otherwise there may be an explosion due to the heat generated.*) After ca. 1.5 h, the reaction mixture was warmed to 60–70 °C and a solution of methyl iodide (80 mmol) in dry THF (20 mL) was added slowly and the resulting mixture was kept stirring for another 1.5 h. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate (500 mL). The organic solution was washed with brine ($3 \times 150 \text{ mL}$) and dried over anhydrous magnesium sulfate. After removal of solvent, the residue was chromatographed on a silica gel column with a mixture of petroleum ether and ethyl acetate (5:1) as the mobile phase to give pure N^2,N^6 -bis(6-bromopyridin-2-yl)- N^2,N^6 -dimethylpyridine-2,6-diamine (**6**, 7.54 g, 84 %) or N^1,N^3 -bis(6-bromopyridin-2-yl)- N^1,N^3 -dimethylbenzene-1,3-diamine (**7**, 6.98 g, 78 %).

N^2,N^6 -Bis(6-bromopyridin-2-yl)- N^2,N^6 -dimethylpyridine-2,6-diamine (6**):** m.p. 109–110 °C (pale yellow crystals from a mixture of petroleum ether and ethyl acetate (4:1)); ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 7.71$ (t, $J = 8.0 \text{ Hz}$, 1H), 7.54 (t, $J = 7.9 \text{ Hz}$, 2H), 7.24 (d, $J = 8.3 \text{ Hz}$, 2H), 7.11 (d, $J = 7.5 \text{ Hz}$, 2H), 6.95 (d, $J = 8.0 \text{ Hz}$, 2H), 3.45 (s, 6H) ppm; ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 157.3, 155.3, 140.4, 140.1, 138.9, 119.9, 112.9, 109.0, 36.2$ ppm; MS (EI): m/z : 449 (100), 447 $[M]^+$ (56), 291 (51), 277 (36), 264 (40); elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{15}\text{N}_5\text{Br}_2$: C 45.46, H 3.37, N 15.59; found: C 45.56, H 3.35, N 15.53.

N^1,N^3 -Bis(6-bromopyridin-2-yl)- N^1,N^3 -dimethylbenzene-1,3-diamine (7**):** m.p. 124–125 °C (pale yellow crystals from a mixture of petroleum ether and ethyl acetate (5:1)); ^1H NMR (300 MHz, CDCl_3): $\delta = 7.45$ (t, $J = 7.9 \text{ Hz}$, 1H), 7.20 (t, $J = 7.7 \text{ Hz}$, 2H), 7.18 (s, 1H), 7.13 (dd, $J = 8.0, 2.0 \text{ Hz}$, 2H), 6.80 (d, $J = 7.4 \text{ Hz}$, 2H), 6.54 (d, $J = 8.3 \text{ Hz}$, 2H), 3.48 (s, 6H) ppm; ^{13}C NMR (75 MHz, CDCl_3): $\delta = 158.4, 147.1, 140.0, 138.9, 130.9, 124.0, 123.2, 116.5, 107.1, 38.5$ ppm; MS (EI): m/z : 450 (49), 449 (48), 448 (100), 447 (70), 446 $[M]^+$ (50), 445 (31), 369 (32), 367 (42), 287 (35); elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{Br}_2$: C 48.24, H 3.60, N 12.50; found: C 48.32, H 3.54, N 12.50.

General procedure for the synthesis of methylazacalix[n]pyridines and methylazacalix[m]arene[n]pyridines: Under argon protection, a mixture of trimer **6** or **7** (1 mmol), diamine **8** or **9** (1 mmol), $[\text{Pd}_2(\text{dba})_3]$ (92 mg, 0.1 mmol), dppp (82 mg, 0.2 mmol), and sodium *tert*-butoxide (288 mg, 3 mmol) in anhydrous 1,4-dioxane (250 mL) was warmed (or heated at reflux) for a period of time (Table 1 and Supporting Information). When **6** or **7** was consumed, as monitored by TLC, the reaction was quenched by cooling down to room temperature and the mixture was filtered through a Celite pad. The filtrate was acidified to pH 7–8 with aqueous hydrochloric acid (2 M). After removal of the solvent, the residue was dissolved in dichloromethane (45 mL) and washed with brine ($3 \times 15 \text{ mL}$), the aqueous phase was re-extracted with dichloromethane ($3 \times 20 \text{ mL}$), and the combined organic phase was dried over anhydrous sodium sulfate. Basic aluminium oxide column chromatography, with elution with a mixture of petroleum ether and ethyl acetate (10:1) to a mixture of petroleum ether and ethyl acetate (2:1) with 0.2 % of ammonium, gave pure products **10**, **11**, and **12**, or **13** and **14**.

Methylazacalix[4]pyridine **10:** m.p. 263–264 °C; ^1H NMR (600 MHz, CD_2Cl_2): $\delta = 7.42$ (t, $J = 7.8 \text{ Hz}$, 4H), 6.40 (d, $J = 7.8 \text{ Hz}$, 8H), 3.24 (s, 12H) ppm; ^{13}C NMR (75 MHz, CDCl_3): $\delta = 159.1, 138.4, 108.5, 36.6$ ppm; MS (MALDI-TOF): m/z : 425.3 $[M+H]^+$; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{24}\text{N}_8$: C 67.90, H 5.70, N 26.40; found: C 67.89, H 5.72,

N 26.41. Recrystallization from acetonitrile gave single crystals suitable for X-ray diffraction analysis.

Methylazacalix[8]pyridine 11: m.p. 117–118 °C; ^1H NMR (600 MHz, CD_2Cl_2): δ = 7.43 (t, J = 7.8 Hz, 8H), 6.76 (d, J = 8.4 Hz, 16H), 3.52 (s, 24H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ = 156.0, 139.0, 107.2, 36.1 ppm; MS (MALDI-TOF): m/z : 848.8 $[M+1]^+$; elemental analysis calcd (%) for $\text{C}_{48}\text{H}_{48}\text{N}_{16}$: C 67.90, H 5.70, N 26.40; found: C 67.66, H 5.71, N 26.37. Slow evaporation of solvent from the solution of **11** in a mixture of hexane and ethyl acetate (6:1) gave X-ray quality single crystals.

Linear pentamer 12: m.p. 72–73 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.30–7.39 (m, 5H), 6.73–6.81 (m, 6H), 6.52 (d, J = 7.9 Hz, 2H), 5.98 (d, J = 7.9 Hz, 2H), 4.47 (s, 2H), 3.60 (s, 6H), 3.56 (s, 6H), 2.90 (s, 6H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ = 158.9, 156.9, 156.5, 156.4, 156.3, 138.6, 137.6, 137.6, 106.2, 106.1, 105.9, 103.6, 98.4, 35.6, 35.6, 29.2 ppm. IR (KBr): ν = 3285, 1599, 1562, 1408 cm^{-1} ; HRMS (FT-ICR): found 562.3141 $[M+H]^+$; $\text{C}_{31}\text{H}_{36}\text{N}_{11}$ requires 562.3149.

Methylazacalix[2]arene[2]pyridine 13: m.p. 245–246 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.42 (t, J = 8.0 Hz, 2H), 7.05 (t, J = 7.8 Hz, 2H), 6.74 (d, J = 7.9 Hz, 4H), 6.66 (s, 2H), 6.02 (d, J = 8.0 Hz, 4H), 3.18 (s, 12H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ = 38.9, 95.0, 124.9, 126.6, 128.9, 138.8, 148.9, 158.3 ppm; MS (EI): m/z : 422 $[M]^+$ (100%), 211 (24); elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{26}\text{N}_6$: C 73.91, H 6.20, N 19.89; found: C 74.25, H 6.30, N 19.85.

Methylazacalix[4]arene[4]pyridine 14: m.p. 209–210 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.46 (t, J = 8.0 Hz, 4H), 7.35 (s, 4H), 7.07–7.13 (m, 12H), 5.97 (d, J = 8.0 Hz, 8H), 3.49 (s, 24H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ = 38.9, 98.8, 122.7, 125.2, 131.1, 138.8, 148.6, 158.2 ppm; MS (MALDI-TOF): m/z : 845.8 $[M+1]^+$; elemental analysis calcd (%) for $\text{C}_{52}\text{H}_{52}\text{N}_{12}$: C 73.91, H 6.20, N 19.89; found: C 74.16, H 6.30, N 20.07.

Preparation of X-ray quality single crystals: Single crystals of monoprotated **10** were obtained by diffusing diethyl ether vapor into a solution of **10** (10 mg) and $\text{Fe}(\text{ClO}_4)_3$ (10 mg) in DMF (2 mL) at 15–20 °C, while single crystals of **10**·2HClO₄ were cultivated simply by evaporating the solvent from a clear solution of **10** in aqueous HClO₄ solution (2M) at room temperature.

BiCl_3 (10 mg) and aqueous HClO₄ solution (1M, 15 mL) were added consecutively to a solution of **10** (10 mg) in acetonitrile (10 mL). The mixture was warmed for 5 min and was then filtered. Slow evaporation of solvent from the clear solution at 20 °C afforded single crystals of triprotonated **10**.

For the preparation of methylazacalix[4]pyridine complex with oxalic acid, **10** (20 mg) was first dissolved in dichloromethane (5 mL). Titanium oxalate (20 mg) and methanol (15 mL) were added, and the resulting mixture was warmed for 5 min and filtered. Hexane (10 mL) was then added to the filtrate to give a clear solution. Slow evaporation of the solvent at 20 °C gave single crystals of **10**·2HO₂CCO₂H·H₂O.

Single crystals of $[\text{Cu}(\text{10})(\text{PF}_6)_2 \cdot 0.5\text{CH}_2\text{Cl}_2]$ were obtained by treatment of **10** (25 mg, 0.06 mmol) with $[\text{Cu}(\text{NCCCH}_3)_4]\text{PF}_6$ (22 mg, 0.06 mmol) in a mixture of dichloromethane and methanol. After having been heated at reflux overnight, the solution was cooled down to room temperature. Slow evaporation of solvent at room temperature afforded red crystals. To cultivate single crystals of monoprotated methylazacalix[2]arene[2]pyridine **[H-13]**ClO₄·CH₂Cl₂, **13** (10 mg) was first dissolved in dichloromethane (5 mL). After addition of methanol (5 mL) and aqueous HClO₄ solution (1M, 5 mL), *n*-hexane (10 mL) was added. Slow evaporation of solvent at 8–10 °C gave crystals suitable for X-ray diffraction analysis.

Single crystals of diprotonated methylazacalix[2]arene[2]pyridine were obtained from the evaporation of solvent from a solution of **13** (10 mg) in HI (40%, 1 mL), methanol (2 mL), and *n*-hexane (10 mL) at 8–10 °C. CCDC-600392, CCDC-600397, CCDC-600394, CCDC-600393, CCDC-600395, CCDC-600396, CCDC-600391, and CCDC-601458 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

The work was supported by funds from the National Natural Science Foundation of China, the Ministry of Science and Technology of China, and the Chinese Academy of Sciences. We thank Professor Yun-Dong Wu of Beijing University for helpful discussions.

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Received: March 17, 2006
Published online: July 18, 2006