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Synthesis, Structure, and Reactions of NH-Bridged Calix[*m*]arene[*n*]pyridines

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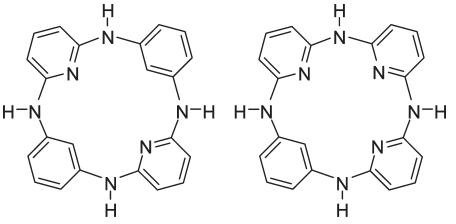

NH-bridged calix[m]arene[n]pyridines (m=n=2; m=1, n=3)

NH-bridged calix[1]arene[3]pyridine and calix[2]arene[2]pyridine were synthesized readily from efficient deprotection of *N*-Boc groups of NBoc-bridged calix[*m*]arene[*n*]pyridine derivatives which were prepared by a macrocyclic coupling reaction between NBoc-linked trimers and 1,3-phenylenediamine. In the solid state, calix[2]arene[2]pyridine adopted the flattened saddle conformation, while NH-bridged calix[1]arene[3]pyridine gave a slightly twisted 1,3-alternate conformer. In both cases, all NH bridges formed partial conjugation with both pyridine and benzene rings, whereas in solution they gave symmetric conformational structures in which the conjugation of bridging NH units with pyridine ring was stronger than with benzene ring. In the presence of NaH, NH-bridged calix[2]arene[2]pyridine reacted efficiently with methyl iodide and allyl bromide to afford the corresponding *N*-alkylated products in almost quantitative yield. Upon treatment of NH- and NMe-bridged calix[2]arene[2]pyridines with CF_3CO_2D and $CuBr_2$, deuteration and bromination reactions took place selectively on the pyridine ring, producing respectively the pyridine ring-deuterated and -brominated macrocyclic products.

Introduction

The design and synthesis of novel and functional macrocyclic host molecules have always been one of the driving forces to promote the major advances of supramolecular science.[1] One of the well-known examples is the development of supramolecular chemistry based on calix[*n*]arenes since the pioneering work of Gutsche in the 1970s.[2] Because of their easy availability, unique conformational structures, and molecular recognition properties, calix[*n*]arenes have become an indispensable part of supramolecular chemistry.[3] Heterocalixaromatics,[4−8] heteroatom-bridged calixaromatics,

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have attracted considerable interest in recent years. Introduction of heteroatoms such as nitrogen,[5] oxygen,[6] and sulfur[7] into the bridging positions of calixaromatics leads to the emergence of a new generation of macrocyclic host molecules in comparison to the conventional calix[*n*]arenes. Because the heteroatoms can adopt different electronic configurations and form different degrees of conjugation with their 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, tetramethylazacalix[4]pyridine has been found to give cavities of different sizes to interact with the different guest species.[5e,5f,5l,5o] 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 nitrogen-bridged calixpyridines, for instance, are able to interact with fullerenes C_{60} and C_{70},[5d,5e,5m,5n] whereas the oxygen-bridged calix[2]arene[2]triazines complex halides through anion$-\pi$ interactions.[9] Furthermore, the heterocalixaromatics are readily functionalized not only on the aromatic rings[10] but also on the bridging positions,[11] allowing the construction of polyfunctionalized host molecules. Moreover, the powerful and efficient fragment coupling approaches would facilitate the generation of numerous heterocalixaromatics when the combinations of varied (hetero)aromatic dinucleophilic and dielectrophilic reactants are employed.[4]

Although a variety of heterocalixaromatics have been reported, the NH-bridged calixaromatics still remain largely unexplored. Only several NH-bridged calixaromatics have been synthesized from the reaction of 1,3-phenylenediamines with very reactive dielectrophiles such as cyanuric chloride and 1,5-difluoro-2,4-dinitrobenzenes. For example, using the fragment coupling method, we[6a] previously prepared NH-bridged calix[2]arene[2]triazines from 1,3-phenylenediamine and cyanuric chloride. Siri[12] and Konishi[13] independently reported the synthesis of NH-bridged calix[4]arenes by reacting of 1,3-phenylenediamine with 1,5-difluoro-2,4-dinitrobenzenes. The use of 1,3-dibromobenzenes and 2,6-dibromopyridines as dielectrophiles in the reaction with 1,3-phenylenediamine led to no or very low yields of NH-bridged calixaromatics.[5h] Very recently, Rajca and co-workers[14] reported the synthesis of NH-bridged calix[n]arenes from exhaustive debenzylayion of NBn-bridged calix[*n*]arenes.

For years, we have been investigating heterocalixpyridine derivatives because of their interesting cavity structures and versatile properties in recognizing various metal cations and neutral molecules.[4a,5d−5f,5l−5o] It is desirable to have the NH-bridged calixpyridine derivatives in order to understand the substituent effect of the bridging nitrogen atoms on the structure and property of azacalixpyridines. We report herein the synthesis of NH-bridged calix[1]arene[3]pyridine and calix[2]arene[2]pyridine from *N*-Boc-protected calix[1]arene[3]pyridine and calix[2]arene[2]pyridine. Their conformational structures, along with those of NBoc-linked analogues, will be presented. We will also show the *N*-alkylation reactions with methyl iodide and allyl bromide and unexpected selective deuteration and bromination reactions of NH-bridged calix[2]arene[2]pyridine with CF_3CO_2D and $CuBr_2$, respectively.

Results and Discussion

Synthesis. We initially attempted a straightforward synthesis of NH-bridged calix[4]pyridine utilizing a macrocyclization coupling approach. Following our previous method[5d,5e] for the synthesis of NMe-bridged calix[4]pyridine, the Pd-catalyzed reaction between N^2,N^6-bis(6-bromopyridin-2-yl)pyridine-2,6-diamine **1a** and 2,6-diaminopyridine **2a** was performed in refluxing toluene (Scheme 1). The reaction proceeded slowly. The increase of catalyst loading [$Pd_2(dba)_3$ 16 mol % and dppp 40 mol %] and the use of benzo-18-crown-6 did not improve the conversion of starting materials. Unfortunately, instead of the desired NH-bridged calix[4]pyridine, the reaction produced only a mixture of inseparable linear oligomers. Under the same catalytic conditions, the reaction of N^1,N^3-bis(6-bromopyridin-2-yl)benzene-1,3-diamine **1b** with 1,3-phenylenediamine **2b** gave a mixture of products, and among them the target molecule NH-bridged calix[2]arene[2]pyridine **3b** was isolated in 12% yield. To enhance the efficiency for the formation of macrocyclic product **3b**, template effects using alkali and alkaline earth metal ions, Cu^{2+} and Ag^+, high dilution reaction conditions, and other solvents such as tetrahydrofuran (THF) were examined. Disappointingly, no noticeable improvement was observed. It should also be pointed out that the isolation of **3b** from the linear oligomeric mixtures was very tedious and not practical, requiring iterative column chromatography.

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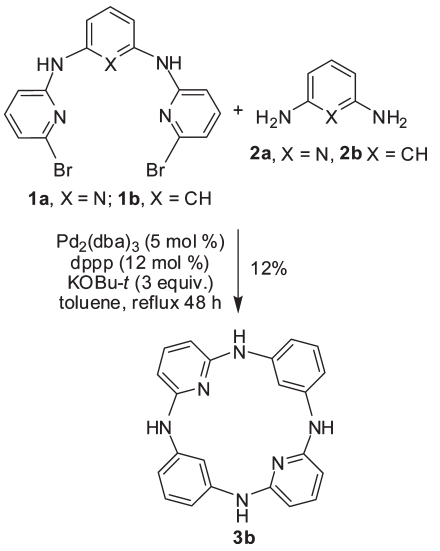
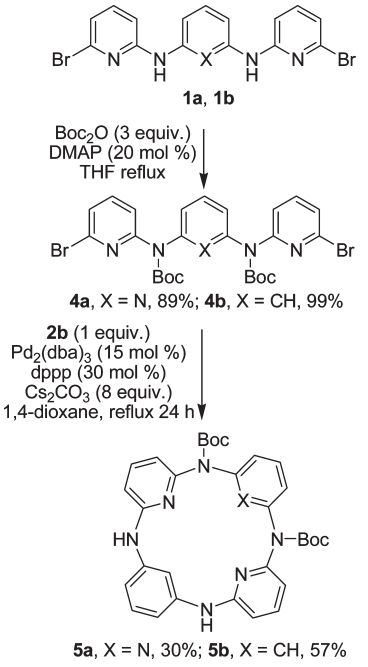
SCHEME 1. Attempted Synthesis of NH-Bridged Calixpyridines



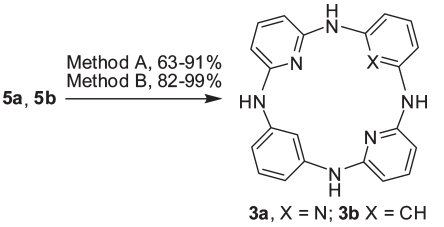
Inspired by the synthesis of NH-bridged calix[*m*]arenes from exhaustive *N*-debenzylation of NBn-bridged calix[*m*]-arenes,[14] we then investigated the synthesis of NH-bridged calixpyridines using the *N*-*tert*-butyloxycarbonyl (*N*-Boc) protection and deprotection strategy. The reaction of **1** with Boc_2O in the presence of 4-dimethylaminopyridine (DMAP) proceeded smoothly in refluxing THF to afford *N*-Boc-protected products **4a** and **4b** in 89% and 99% yields, respectively. To our delight, catalyzed by $Pd_2(dba)_3$/dppp in the presence of an excess amount of cesium carbonate, *N*-Boc-protected linear trimer **4a** was found to react with 1,3-phenylenediamine **2b** in refluxing 1,4-dioxane to afford azacalix[1]arene[3]pyridine **5a** in 30% yield. Analogously, azacalix[2]arene[2]pyridine **5b** was obtained nicely in a higher chemical yield when **4b** was treated with **2b** (Scheme 2). To prepare azacalix[4]pyridine, the reaction of **4a** with 2,6-diaminopyridine **2a** was tested. Under the identical catalytic conditions, however, no reaction took place between **4a** and **2a**. This is probably attributable to the lower nucleophilicity of 2,6-diaminopyridine **2a** than that of 1,3-phenylenediamine **2b**. Employment of forcing reaction conditions such as using potassium *tert*-butoxide as a base did not effect the formation of macrocyclic compound either. Instead, we observed the formation of **1a** from *N*-deprotection of **4a**, along with the formation of a mixture of linear oligomers. The higher tendency of *N*-Boc-protected trimer **4** than trimer **1** to undergo macrocyclic coupling reaction with 1,3-phenylenediamine **2b** was intriguing. While the exact reason awaits further study, it is most likely that the presence of bulk *tert*-butyloxycarbonyl groups on the linking nitrogen atoms led to the conformation of the linear precursor preferable for cyclization.

Both basic and acidic conditions were applied to remove Boc group from the bridging nitrogen atoms of compounds **5a** and **5b**. When refluxed with a large excess amount of sodium *tert*-butoxide (15−20 equiv) in 1,4-dioxane for 12 h, **5a** and **5b** underwent Boc deprotection from linking nitrogen to produce NH-bridged calix[1]arene[3]pyridine **3a** and calix[2]arene[2]pyridine **3b** in 63% and 91%, respectively. The more efficient Boc cleavage was effected when compounds **5a** and **5b** were refluxed in acetic acid for 12 h,

SCHEME 2. Synthesis of 5a and 5b



SCHEME 3. Synthesis of NH-Bridged Calix[1]arene[3]pyridine 3a and Calix[2]arene[2]pyridine 3b



furnishing NH-bridged calixpyridines **3a** and **3b** in excellent yields (Scheme 3).

Structure. NH-bridged calix[*m*]arene[*n*]pyridine products are crystalline products, and they gave high-quality single crystals suitable for X-ray diffraction analysis (Table 1). The X-ray crystal structures revealed that introduction of NH linkage into the bridging positions of calix[*m*]arene[*n*]pyridines led to interesting conformational structures in the solid state. We have previously shown that tetramethylazacalix[2]-arene[2]pyridine, NMe-bridged calix[2]arene[2]pyridine, gives a slightly twisted 1,3-alternate conformation with two benzene rings being face-to-face parallel and two pyridine rings being edge-to-edge aligned.[5d] In contrast to tetramethylazacalix[2]-arene[2]pyridine, both discrete NH-bridged calix[2]arene[2]-pyridine molecules **3b**, which only differ slightly in bond lengths and bond angles (Figure S1, Supporting Information), in a single unit cell adopted the flattened saddle conformation (Figure 1). While all bridging nitrogen atoms only form conjugations with their adjacent pyridine rings in NMe-bridged calix[2]arene[2]pyridine, all NH bridges in **3b**, which are sp^2 electronically configured, form partial conjugation with both pyridine and benzene rings. As judged by the mean distances between bridging nitrogen and the pyridine carbon (d = 1.402 Å) and between bridging nitrogen and benzene carbon (d = 1.408 Å), the conjugation between

TABLE 1. X-ray Crystallographic Data of NH-Bridged Calix[*m*]arene[*n*]pyridines

compd	**3b**	**3a**·$4C_4H_8O_2$	**5b**	**5a**·H_2O
emp formula	C_{22} H_{18} N_6	C_{37} H_{49} N_7 O_8	C_{32} H_{34} N_6 O_4	C_{31} H_{35} N_7 O_5
M_r	366.42	719.83	566.65	585.66
cryst size (mm^3)	0.42 × 0.30 × 0.29	0.22 × 0.20 × 0.10	0.63 × 0.55 × 0.05	0.41 × 0.11 × 0.02
cryst system	triclinic	tetragonal	monoclinic	triclinic
space group	*P*-1	*I*4(1)/*a*	*P*2(1)/*c*	*P*-1
a (Å)	8.3972(17)	15.300(2)	9.4503(19)	9.3910(19)
b (Å)	10.175(2)	15.300(2)	25.929(5)	11.235(2)
c (Å)	21.221(4)	14.684(3)	23.646(5)	15.836(3)
α (deg)	98.76(3)	90	90	78.30(3)
β (deg)	101.25(3)	90	96.66(3)	86.16(3)
γ (deg)	97.86(3)	90	90	67.25(3)
D (g/cm^3)	1.406	1.391	1.308	1.289
Z	4	4	8	2
T (K)	173(2)	113(2)	293(2)	293(2)
R1, wR2 [$I > 2\sigma(I)$]	R1 = 0.0627, wR2 = 0.1436	R1 = 0.0470, wR2 = 0.1156	R1 = 0.0571, wR2 = 0.1195	R1 = 0.1400, wR2 = 0.1588
R1, wR2 [all data]	R1 = 0.0829, wR2 = 0.1529	R1 = 0.0512, wR2 = 0.1190	R1 = 0.1167, wR2 = 0.1407	R1 = 0.2779, wR2 = 0.1929
quality of fit	1.123	1.075	0.945	1.190

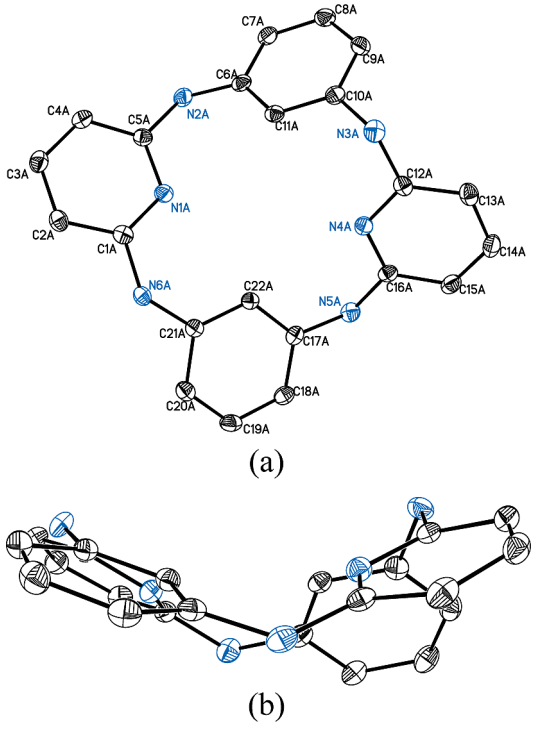


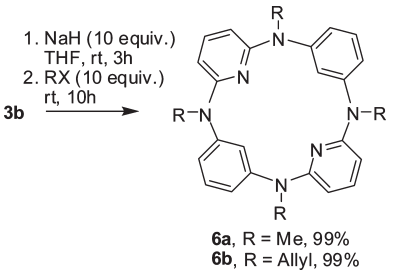
FIGURE 1. X-ray crystal structure of NH-bridged calix[2]arene[2]pyridine **3b**: (a) top view and (b) side view. Only one of the two discrete molecules in a single unit cell is shown. Selected bond lengths (Å): N(2A)−C(6A) 1.403(4); N(2A)−C(5A) 1.404(4); N(3A)−C(12A) 1.412(4); N(3A)−C(10A) 1.440(3); N(5A)−C(16A) 1.390(4); N(5A)−C(17A) 1.407(3); N(6A)−C(1A) 1.389(3); N(6A)−C(21A) 1.401(3). (Hydrogen atoms are omitted for clarity.)

bridging nitrogen and pyridine ring is slightly stronger than that between bridging nitrogen and benzene ring. The formation of stronger conjugation of bridging nitrogen atoms with pyridine rings led to the higher reactivity of pyridine rings than benzene rings in aromatic electrophilic substitution reactions (vide infra). The tendency for NH-bridged calix[2]arene[2]pyridine **3b** to form a more flattened conformation in comparison to 1,3-alternate tetramethylazacalix[2]arene[2]pyridine is most probably due to the least steric effect of NH linkages. In the case of crystal structure of NH-bridged calix[1]arene[3]pyridine **3a**, which was illustrated in Figure S2 (see the Supporting Information), the macrocycle adopted a flattened and slightly twisted 1,3-alternate conformation with an approximate S_4 symmetry. All nitrogen atoms in the linking positions again formed partial conjugations with both adjacent aromatic rings.

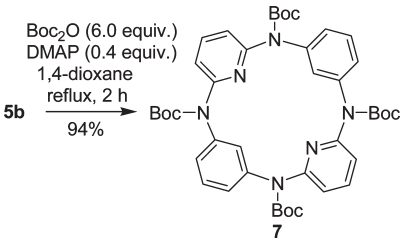
The solid-state structures of NH-bridged calix[2]arene[2]pyridine **5b** and calix[1]arene[3]pyridine **5a** were also worth addressing. Bearing two Boc protection groups on the bridging nitrogen atoms, both macrocycles gave a partial cone conformation (Schemes S3 and S4, Supporting Information). All nitrogen atoms adopted an sp^2 electronic configuration. The bridging nitrogen atoms attached by Boc formed strong conjugation with the carbonyl group rather than aromatic rings, and two bulky Boc groups were *trans*-orientated. While the partial conjugation between one of the NH bridges and its linking aromatic rings was observed, the other NH linking unit formed strong conjugation with its two neighboring aromatic rings to yield a nearly planar Ar−NH−Ar segment (Schemes S3 and S4, Supporting Information).

Although in the solid state NH-bridged calix[m]arene[n]pyridines **3** and **5** exist in certain conformations with different conjugation systems being observed, these macrocycles may not be able to retain these stable conformational structures in the solution. In both ^1H and ^{13}C NMR spectra, only one set of proton and carbon resonance signals was observed for NH-bridged calix[m]arene[*n*]pyridines **3** and **5** in solution. For example, NH-bridged calix[2]arene[2]pyridine **3b** gives two pairs of coupled triplet and doublet peaks of the protons of *meta*-substituted benzene and 2,6-disubstituted pyridine rings, whereas three pairs of coupled triplet and doublet peaks corresponding to protons of one 2,6-disubstituted pyridine, one *meta*-substituted benzene, and another two identical 2,6-disubstituted pyridine rings were observed in **3a**. In the case of Boc-protected NH-calix[*m*]arene[*n*]pyridines **5a** and **5b**, only one type of *tert*-butyl group was evidenced by ^1H and ^{13}C NMR spectra. These NMR spectral characteristics indicated that all NH-bridged calix[*m*]arene[*n*]pyridine compounds **3** and **5** might adopt highly symmetric conformational structures in solution. Most probably, these macrocycles are very fluxional in solution, and the rates of interconversion of various conformational structures might be very rapid relative to the NMR time

SCHEME 4. *N*-Alkylation of NH-Bridged Calix[2]arene[2]pyridine 3b



SCHEME 5. Synthesis of All NBoc-Bridged Calix[2]arene[2]pyridine 7



scale. The high conformational mobility of these NH-bridged calix[*m*]arene[*n*]pyridines is most likely due to the lack of steric hindrance and intramolecular hydrogen bonds, both being key factors in stabilizing conformational structures of conventional calix[*n*]arenes[2] in solution. The stability gained from the conjugation effect of the linking nitrogen atoms with their adjacent aromatic rings seems insufficient to prevent the rotation of aromatic rings around the *meta*−*meta* axes or through the annulus. It is interesting to note that the protons at 3- and 5-positions of the pyridine ring in **3b** appeared at 6.33 ppm, upfield shifted in comparison to the protons of the benzene ring in **3b** which resonated at 6.58 ppm. That is indicative of the stronger conjugation effect between NH-bridges and pyridine rings than between NH-bridges and benzene rings in **3b** in solution.

Reaction. To explore the applications of heterocalixaromatics in molecular recognition and molecular assembly, constructions of functional macrocycles are highly desirable. Although a large number of heterocalixaromatics have been prepared in recent years, the functionalized heterocalixaromatics,[4,6n,10,11] the macrocycles which are installed with functional groups for molecular recognition and assembly, are still very rare. We[10a−10c] have previously synthesized tetraoxacalix[2]arene[2]triazines that contain metal ion-chelating ligands, azacrown ethers, and fluorescence moieties at the larger rim. Dehaen and co-workers[6n] have also reported the larger rim functionalization of tetraoxacalix[2]arene[2]pyrimidine with a benzo-crown ether and with L-cysteine ethyl ester groups. Very recently, direct and diverse functionalizations of benzene ring of tetramethylazacalix[1]arene[3]pyridine were achieved through the arene C−H activation by copper(II).[10e] NH-bridged calix[*m*]arene[*n*]pyridines obtained are nice substrates for further functionalizations because the chemical manipulations can be implemented on both aromatic rings and the bridging nitrogen atoms.

To demonstrate the functionalization on the bridge positions, we first carried out the *N*-alkylation reaction of NH-bridged calix[2]arene[2]pyridine **3b** (Scheme 4). With the aid of sodium hydride, compound **3b** underwent efficient *N*-methylation reaction with methyl iodide at ambient temperature to produce tetramethylazacalix[2]arene[2]pyridine **6a** in 99% yield. It is noteworthy that compound **6a** was previously prepared from a 3 + 1 fragment coupling reaction between N^1,N^3-bis(6-bromopyridin-2-yl)-N^1,N^3-dimethylbenzene-1,3-diamine and N^1,N^3-dimethylbenzene-1,3-diamine. The chemical yield is around 20%, and the separation is tedious.[5d] The current method, however, offered an easy entry to **6a** in an improved yield. Under the identical conditions, four allyl groups were introduced successfully onto the bridging positions of **3b** to furnish product **6b** quantitatively (Scheme 4). Product **6b** should be amenable to further functionalizations using various functional group transformations of allyl group. Another example of *N*-functionalization was illustrated in Scheme 5. Starting with *N*-Boc protected NH-calix[2]arene[2]pyridine **5b**, the *N*-acylation reaction with Boc_2O afforded all NBoc-bridged calix[2]arene[2]pyridine in 94% yield.

Considering the delocalization of electrons of bridging nitrogen atoms into the aromatic rings due to conjugation effect, electrophilic aromatic substitution reactions of azacalix[2]arene[2]pyridines **3b** and **6a** were investigated. To understand the reactivity of electrophilic aromatic substitution reactions, deuteration of **3b** and **6a** was conducted and monitored by ^{1}H NMR spectroscopy using CF_3CO_2D as a deuterating reagent. As illustrated in Figure 2, interaction of both NH- and NMe-bridged calix[2]arene[2]pyridines with CF_3CO_2D led to the gradual disappearance of doublet signals at 6.57 ppm for **3b** and at 6.47 ppm for **6a**. Concomitantly, the triplet signals at 7.86 ppm for **3b** and at 8.02 ppm for **6a** (see the Supporting Information) changed into a mixture of triplet, doublet, and singlet signals of different intensity, which appeared like a quintet peak and then a singlet peak (Figure 2a). On the basis of intensity of doublet signals at 6.57 ppm, the deuteration of **3b** finished 30% in 10 min and 98% in 5 h. Deuteration proceeded slower for **6a**, with 59%, 84%, and 96% deuteration being observed in 2, 5, and 12 h, respectively. Surprisingly, careful scrutiny of ^{1}H NMR spectra revealed that it was the protons of pyridine rings that underwent deuteration at the 3 and 5 positions, and the protons of the benzene rings remained intact under the reaction conditions. The unusual reaction outcomes, viz. pyridine moiety showing higher reactivity than benzene moiety in deuteration with CF_3CO_2D, were intriguing. It has been shown that, in the crystalline state and in solution, bridging nitrogen atoms in both NH-bridged calix[2]arene[2]pyridine **3b** (vide supra) and NMe-bridged calix[2]arene[2]pyridine **6a**[5e] formed stronger conjugation with pyridine rings than with benzene rings. In other words, it is the formation of conjugation between bridging nitrogen atoms and pyridine rings that lead to delocalization of nitrogen lone pair electrons into the pyridine ring. As a consequence, electrophilic aromatic deuteration took place on pyridine rather than benzene rings of azacalix[2]arene[2]-pyridines **3b** and **6a**.

Encouraged by the facile deuteration of the pyridine rings of azacalix[2]arene[2]pyridines, we then tried the bromination of NH- and NMe-bridged calix[2]arene[2]pyridines. Reaction of **3b** and **6a** with *N*-bromosuccinimde (NBS) occurred rapidly at room temperature in organic solvent

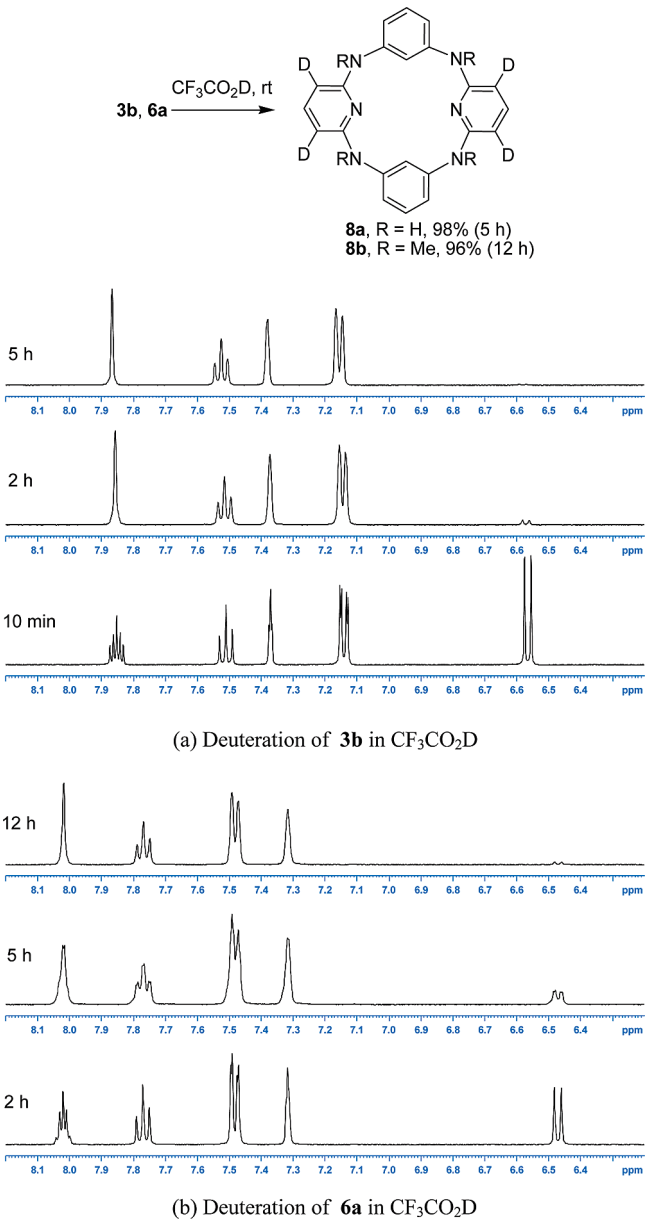
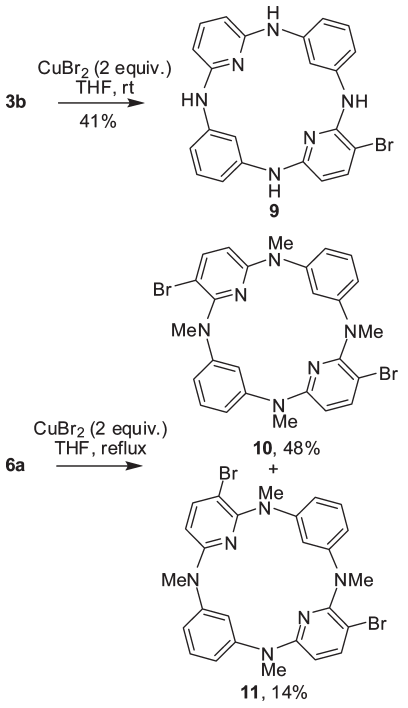


FIGURE 2. Deuteration of azacalix[2]arene[2]pyridines **3b** and **6a**.

such as CH_2Cl_2, CH_3CN and DMF. Unfortunately, the reaction gave a mixture of products which were difficult to separate using column chromatography. The reaction was not improved either when acids including CH_3CO_2H, CF_3CO_2H and *para*-toluenesulfonic acid were used to deactivate the pyridine moieties. We then found that $CuBr_2$ was an efficient halogenation reagent[15] to brominate azacalix[2]arene[2]-pyridines. Under very mild conditions such as in THF at ambient temperature, interaction of NH-bridged calix[2]arene [2]pyridine **3b** with $CuBr_2$ led to the monobromination on the pyridine ring of the macrocycle to afford **9** as the major product in 41% yield (Scheme 6). The reaction between NMe-bridged calix[2]arene[2]pyridine **6a** with $CuBr_2$ did not proceed at room temperature. At an elevated temperature

SCHEME 6. Bromination of Azacalix[2]arene[2]pyridines 3b and 6a



such as in refluxing THF, reaction gave a mixture of products, and among which the dibrominated products **10** and **11** were isolated in 48% and 14% yield, respectively (Scheme 6). The same reaction performed in other solvents including $CHCl_3$, 1,4-dioxane, acetonitrile, and DMF led to much lower chemical yields of products. The easier bromination of NH-bridged calix[2]arene[2]pyridine **3b** than NMe-bridged calix[2]arene[2]pyridine **6a** is consistent with the fact that the former macrocycle forms better conjugation between bridging nitrogen atoms and pyridine rings in solution.

Conclusion

In summary, we have developed an efficient method for the synthesis of all NH-bridged calix[1]arene[3]pyridine and calix-[2]arene[2]pyridine from deprotection of *N*-Boc groups of NBoc-bridged calix[*m*]arene[*n*]pyridine derivatives which were prepared by macrocyclic coupling reaction between NBoc-linked trimers and 1,3-phenylenediamine. In the solid state, calix[2]arene[2]pyridine adopted the flattened saddle conformation, while NH-bridged calix[1]arene[3]pyridine gave a slightly twisted 1,3-alternate conformer. In both cases, all NH bridges formed partial conjugation with both pyridine and benzene rings, whereas in solution they gave symmetric conformational structures in which the conjugation of bridging NH units with pyridine ring was stronger than with benzene ring. We have also shown that NH-bridged calix[2]-arene[2]pyridine was able to undergo efficient reactions with alkyl halides and $CuBr_2$ to afford, respectively, the bridging *N*-functionalized and the pyridine ring-functionalized azacalix [2]arene[2]pyridine derivatives. The easy preparation of NH-bridged calixaromatics and their efficient reactions on bridging NH units and on aromatic rings would open a new avenue to the diverse functionalized macrocyclic host molecules useful in supramolecular chemistry.

(15) Use of $CuBr_2$ as a bromination reagent was reported in the literature. (a) Nonhebel, D. C. *J. Chem. Soc.* **1963**, 1216. (b) Kodomari, M.; Satoh, H.; Yoshitomi, S. *J. Org. Chem.* **1988**, *53*, 2093 and references cited therein.

Experimental Section

General Procedure for the Synthesis of *N*-Boc-Protected Linear Trimers 4a and 4b. To a mixture of NH-linked trimer **1a** or **1b** (100 mmol), which was prepared according to a literature method,[5e] and DMAP (20 mmol) in THF (500 mL) was added slowly $(Boc)_2O$ (300 mmol) at room temperature. After release of the gas evolved, the resulting mixture was refluxed for several hours until the starting material was consumed. The solvent was then removed under vacuum. The residue was dissolved in ethyl acetate (500 mL) and washed with saturated $NaHCO_3$ aqueous solution (3 × 500 mL) and brine (3 × 500 mL). The organic layer was dried over with anhydrous magnesium sulfate. After removal of solvent, the residue was subjected to a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (10:1) to give pure product **4a** or **4b**.

4a: yield 89%; mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (t, J = 8.3 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 1.38 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 82.5, 114.1, 121.6, 125.6, 139.1, 139.2, 152.0, 152.3, 154.1; IR (KBr) ν 2980 (w), 1725 (s) cm^{-1}; MS (EI) m/z 619 (3), 621(6), 623 (3) $[M]^+$, 519 (5), 521 (10), 523 (5) $[M - Boc]^+$, 419 (50), 421 (100), 423 (50) $[M - 2Boc]^+$. Anal. Calcd for $C_{25}H_{27}Br_2N_5O_4$: C, 48.33; H, 4.38; N, 11.27. Found: C, 48.44; H, 4.45; N 10.95.

4b: yield 99%; mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, J = 7.9 Hz, 2H), 7.44 (dd, J = 0.7 Hz, J = 7.9 Hz, 2H), 7.34 (t, J = 8.1 Hz, 1H), 7.23 (dd, J = 0.6 Hz, J = 7.5 Hz, 2H), 7.13 (dd, J = 2.0 Hz, J = 8.0 Hz, 2H), 7.00 (t, J = 2.0 Hz, 1H), 1.42 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 82.2, 118.7, 124.5, 126.1, 127.2, 128.9, 139.5, 141.5, 153.1, 155.0; IR (KBr) ν 2927 (w), 1720 (s) cm^{-1}; MS (EI) m/z 618 (5), 620 (10), 622 (5) $[M]^+$, 518 (4), 520 (8), 522 (4) $[M - Boc]^+$, 418 (50), 420 (100), 422 (50) $[M - 2Boc]^+$. Anal. Calcd for $C_{26}H_{28}Br_2N_4O_4$: C, 50.34; H, 4.55; N, 9.03. Found: C, 50.26; H, 4.60; N, 8.83.

General Procedure for the Synthesis of NBoc-Bridged Azacalix[*m*]arene[*n*]pyridines 5a and 5b. Under argon protection, a mixture of trimer **4a** or **4b** (2 mmol), benzene-1,3-diamine (2 mmol), $Pd_2(dba)_3$ (276 mg, 0.3 mmol), DPPP (246 mg, 0.6 mmol), and cesium carbonate powder (5.216 g, 16 mmol) in anhydrous 1, 4-dioxane (500 mL) was refluxed for 24 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (15 mL) and washed with brine (3 × 15 mL). The organic phase was dried over with anhydrous magnesium sulfate. The solvent was removed, and the residue was subjected to a basic aluminum oxide column with a mixture of petroleum ether and ethyl acetate (3:1) as eluent to give pure product **5a** or **5b**.

5a: yield 30%; mp 195−196 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.23 (t, J = 2.0 Hz, 1H), 7.83 (s, 2H, deuterium exchangeable), 7.65 (t, J = 7.9 Hz, 1H), 7.56 (t, J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.98 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 7.6 Hz, 2H), 6.56 (d, J = 7.9 Hz, 2H), 6.44 (dd, J = 7.9, J = 2.0 Hz, 2H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, acetone-d_6) δ 156.2, 154.6, 154.2, 153.9, 143.5, 139.3, 139.1, 129.2, 118.1, 113.8, 112.3, 109.8, 109.3, 81.6, 28.3; IR (KBr) ν 3349 (s), 1686 (s), 1590 (s); ESI-MS m/z 568.4 $[M + H]^+$. Anal. Calcd. for $C_{31}H_{33}N_7O_4 \cdot H_2O$: C, 63.58; H, 6.02; N, 16.74. Found: C, 63.86; H, 6.19; N, 16.79.

5b: yield 57%; mp 233−234 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 2H, deuterium exchangeable), 8.75 (s, 1H), 7.79 (s, 1H), 7.61 (t, J = 7.7 Hz, 2H), 7.31−7.30 (m, 3H), 7.16 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 7.3 Hz, 2H), 6.61 (dd, J = 1.9 Hz, J = 8.0 Hz, 2H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.4, 152.7, 152.2, 141.4, 141.1, 139.2, 128.5, 128.1, 123.3, 122.6, 112.8, 112.4, 110.3, 108.4, 80.5, 27.8; IR (KBr) ν 3370 (m), 1696 (s), 1594 (s) cm^{-1}; MALDI-TOF m/z 567.6 $[M + H]^+$, 589.6 $[M + Na]^+$, 605.6 $[M + K]^+$. Anal. Calcd. for $C_{32}H_{34}N_6O_4$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.94; H, 6.21; N, 14.47.

General Procedure for the Synthesis of NH-Bridged Calix[*m*]arene[*n*]pyridines 3a and 3b. *Method A:* A mixture of **5a** or **5b** (1 mmol) and sodium *tert*-butoxide (15 mmol) in anhydrous 1,4-dioxane (100 mL) was refluxed for 12 h. A few drops of water was added slowly to quench the reaction. After filtration, the solvent was removed, and the residue was subjected to a silica gel column with a mixture of petroleum ether and acetone as eluent to give pure product **3a** (63%) or **3b** (91%). *Method B:* A mixture of **5a** or **5b** (1 mmol) in glacial acetic acid (15 mL) was refluxed for 12 h. Then the solvent was removed under vacuum. The residue was subjected to a silica gel column with a mixture of petroleum ether and acetone as eluent to give pure product **3a** (82%) or **3b** (99%).

3a: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.54 (t, J = 2.0 Hz, 1H), 7.71 (s, 2H, deuterium exchangeable), 7.55 (s, 2H, deuterium exchangeable), 7.42 (t, J = 7.8 Hz 1H), 7.35 (t, J = 7.8 Hz, 2H), 6.94 (t, J = 7.8 Hz, 1H), 6.48 (d, J = 7.8 Hz, 1H), 6.41 (dd, J = 7.9 Hz, J = 2.1 Hz, 2H), 6.30 (d, J = 7.9 Hz, 2H), 6.29 (d, J = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 156.8, 156.6, 156.3, 144.4, 139.3, 139.1, 128.7, 112.5, 110.0, 109.8, 105.0, 104.7; IR (KBr) ν 3406 (w), 3295 (w), 1577 (s); ESI-MS m/z 368.2 $[M + H]^+$, 390.2 $[M + Na]^+$, 406.2 $[M + K]^+$. Anal. Calcd. for $C_{21}H_{17}N_7 \cdot 0.5H_2O$: C, 67.01; H, 4.82; N, 26.05. Found: C, 67.48; H, 4.74; N, 26.05.

3b: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.69 (t, J = 2.0 Hz, 2H), 7.57 (s, 4H, deuterium exchangeable), 7.33 (t, J = 7.8, 2H), 7.01 (t, J = 7.9, 2H), 6.57 (dd, J = 2.0 Hz, J = 7.9 Hz, 4H), 6.32 (d, J = 7.8 Hz, 4H); ^{13}C NMR (75 MHz, acetone-d_6) δ 157.4, 144.6, 139.0, 128.9, 113.8, 111.8, 103.4; IR(KBr) ν 3363 (m), 3378 (m), 1591 (s); ESI-MS m/z 367.2 $[M + H]^+$. Anal. Calcd for $C_{22}H_{18}N_6$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.11; H, 5.03; N, 22.84.

General Procedure for *N*-Alkylation of 3b. To a solution of **3b** (1 mmol) in anhydrous THF (100 mL) was added slowly sodium hydride (15−20 mmol). The reaction mixture was refluxed for 3 h. After the solution was cooled to room temperature, methyl iodide or allyl bromide (10 mmol) was slowly added into the mixture during several minutes. The resulting mixture was then refluxed for another 10 h until **3b** was consumed. After being cooled to room temperature, the mixture was filtered through a Celite pad. The solvent was then removed, and the residue was subjected to a silica gel column with petroleum ether and ethyl acetate as eluent (3:1) to give pure product **6a**[5d] or **6b** in 99% yield.

6b: mp 112−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, J = 8.0 Hz, 2H), 7.01 (t, J = 7.9 Hz, 2H), 6.74 (dd, J = 7.9 Hz, J = 2.0 Hz, 4H), 6.66 (t, J = 1.9 Hz, 2H), 5.96 (d, J = 8.0 Hz, 4H), 5.93−5.80 (m, 4H), 5.21 (dd, J = 17.2 Hz, J = 1.6 Hz, 4H), 5.10 (dd, J = 10.2 Hz, J = 1.5 Hz, 4H), 4.12 (d, J = 5.1 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 147.4, 138.6, 134.3, 128.8, 128.7, 126.7, 116.0, 94.7, 54.0; IR (KBr) ν 1570 (s), 1464 (s); MALDI-TOF m/z 527.4 $[M + H]^+$. Anal. Calcd. for $C_{34}H_{34}N_6$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.53; H, 6.60; N, 15.87.

Synthesis of 7. A mixture of **5b** (28.3 mg, 0.05 mmol), Boc_2O (65.4 mg, 0.3 mmol), and DMAP (2.5 mg, 0.02 mmol) in 1,4-dioxane (6 mL) was refluxed for 2 h. Then the solvent was removed and the residue was subjected to a silica gel column with petroleum ether and ethyl acetate (5:1) as eluent to give pure product **7** (36.2 mg, 94%): mp 219−220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dt, J = 1.0 Hz, J = 7.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 4H), 6.99 (d, J = 8.1 Hz, 2H), 6.73 (dd, J = 8.0 Hz, J = 1.9 Hz, 4H), 6.63 (t, J = 1.8 Hz, 2H), 1.39 (s, 36H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 153.1, 141.6, 138.0, 128.3, 127.9, 127.0, 113.8, 81.5, 28.1; IR (KBr) ν 1711 (s); ESI-MS m/z 767.5 $[M + H]^+$, 789.5 $[M + Na]^+$, 805.5 $[M + K]^+$. Anal. Calcd.

for $C_{42}H_{50}N_6O_8$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.79; H, 6.61; N, 10.72.

General Procedure for Bromination of 3b and 6a. A mixture of **3b** or **6a** (0.1 mmol) and $CuBr_2$ (0.2 mmol) in THF (5 mL) was stirred at room temperature or refluxed until reactant **3b** or **6a** was consumed. The solvent was removed, and water (5 mL) was added. The resulting mixture was extracted with dichloromethane (3 × 5 mL). The organic phase was dried over with anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to a silica gel column. For **9**, a mixture of petroleum ether, acetone, and dichloromethane (15/3/2) was used as eluent. For **10** and **11**, a mixture of petroleum ether, ethyl acetate, and dichloromethane (4/1/1) was used as eluent.

9: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H, deuterium exchangeable), 8.34 (s, 1H, deuterium exchangeable), 8.27 (s, 1H, deuterium exchangeable), 8.02 (s, 1H (Ph)), 7.93 (s, 1H (Ph)), 7.65 (d, J = 8.4 Hz, 1H (Py)), 7.34 (t, J = 7.9 Hz, 1H (Py)), 7.32 (s, 1H, deuterium exchangeable), 7.08 (t, J = 8.1 Hz, 1H (Ph)), 7.06 (t, J = 8.2 Hz, 1H (Ph)), 6.66 (d, J = 8.0 Hz, 1H (Ph)), 6.59 (d, J = 8.0 Hz, 1H (Ph)), 6.54−6.49 (m, 2H (Ph)), 6.29 (d, J = 8.4 Hz, 1H (Py)), 6.23 (d, J = 7.8 Hz, 1H (Py)), 6.22 (d, J = 7.8 Hz, 1H (Py)); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.7, 155.5, 154.8, 151.5, 143.0, 142.9, 142.5, 142.1, 141.4, 138.3, 128.4, 128.3, 114.4, 114.2, 113.2, 112.8, 111.8, 109.9, 105.3, 102.1, 102.0, 95.3; IR (KBr) ν 3396 (br), 1591 (s); ESI-MS m/z 447.1 $[M + H]^+$, 469.1 $[M + Na]^+$, 485.1 $[M + K]^+$. Anal. Calcd for $C_{22}H_{17}BrN_6$: C, 59.34; H, 3.85; N, 18.87. Found: C, 59.08; H, 3.91; N, 18.94.

10: ^{1}H NMR (400 MHz, CF_3COOD) δ 8.20 (d, J = 9.6 Hz, 2H), 7.53 (t, J = 8.0 Hz, 2H), 7.00 (d, J = 9.6 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 6.41 (s, 2H), 3.46 (s, 6H), 3.24 (s, 6H); ^{13}C NMR (100 MHz, CF_3COOD) δ 153.2, 151.0, 148.0, 145.4, 140.5, 133.9, 118.1, 113.9, 110.3, 105.3, 40.3, 37.4; IR (KBr) ν 1602 (s), 1572 (s); ESI-MS m/z 581.1 $[M + H]^+$. Anal. Calcd for $C_{26}H_{24}Br_2N_6$: C, 53.81; H, 4.17; N, 14.48. Found: C, 53.58; H, 4.27; N, 14.08.

11: mp 182−183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 8.5 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.77 (dd, J = 1.9 Hz, J = 8.0 Hz, 2H), 6.65 (d, J = 8.5 Hz, 2H), 6.41 (dd, J = 1.9 Hz, J = 8.0 Hz, 2H), 6.15 (s, 1H), 5.60 (s, 1H), 3.14 (s, 6H), 3.00 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.7, 156.3, 148.5, 148.4, 144.1, 129.8, 128.9, 117.8, 116.7, 111.6, 109.6, 108.5, 106.6, 39.4, 38.6; IR(KBr) ν 1573 (s), 1559 (s); ESI-MS m/z 581.1 $[M + H]^+$, 603.1 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{24}Br_2N_6$: C, 53.81; H, 4.17; N, 14.48. Found: C, 53.54; H, 4.09; N, 14.21

Acknowledgment. We thank the Natural Science Foundation of China, Ministry of Science and Technology (2007CB808005) and the Chinese Academy of Sciences for financial support.

Supporting Information Available: Experimental details, ^{1}H and ^{13}C NMR spectra of products, and X-ray structures of **3a**, **3b**, **5a**, and **5b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.