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Synthesis and Highly Selective Bromination of Azacalix[4]pyrimidine Macrocycles

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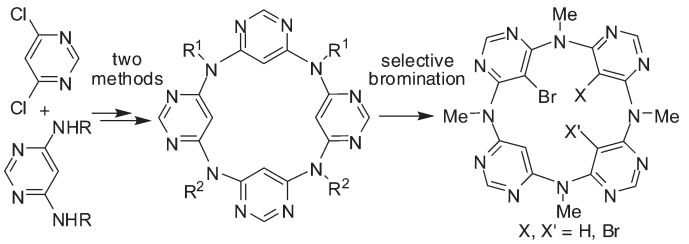

A number of N-substituted azacalix[4]pyrimidines were synthesized by two methods. While straightforward condensation reaction between 4,6-dichloropyrimidine and 4,6-bis(alkylamino)-pyrimidines gave identically N-substituted azacalix[4]pyrimidines in low yields, a general and moderate-to-high yielding 1 + 3 macrocyclic fragment coupling reaction afforded azacalix[4]-pyrimidines that contained either the same or different N-substituents. Upon treatment with *N*-bromosuccinimide (NBS) under controlled conditions, methylazacalix[4]pyrimidine was selectively brominated at lower rim to produce mono-, di-, and tribrominated azacalix[4]pyrimidines in good yields. While azacalix[4]pyrimidine derivatives adopted 1,3-alternate conformation in the solid state, the synthesized macrocycles were fluxional in solution, and the interconversion of various conformational structures was rapid relative to the NMR time scale.

Introduction

As an emerging generation of macrocyclic host molecules in supramolecular chemistry, heterocalixaromatics[1] such as nitrogen-,[1−7] oxygen-,[1,8−13] and sulfur-bridged[14] calixaromatics have been attracting fast growing interest in recent years. Because heteroatoms can adopt different electronic configurations and form various degrees of conjugation with their adjacent aromatic rings, the conformation and the cavity structures of heterocalixaromatics are fine-tuned by the bond lengths and bond angles of the bridging heteroatoms.[1a] For example, by the formation of marginally different conjugations between the bridging nitrogen atoms and their neighboring pyridines, tetramethylazacalix[4]-pyridine[4b] has been found to yield cavities of different sizes to interact with different guest species.[4b,c,e,h] Besides, the various electronic effects of the heteroatoms also regulate the electron density of aromatic rings, producing the cavity of varied electronic features. The tetramethylazacalix[4]-pyridine, for instance, acts as a powerful polydentate ligand

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and hydrogen bond acceptor to recognize metal cations[4c,h] and both aliphatic and aromatic diols,[4e] respectively. Furthermore, the azacalixaromatics are readily functionalized not only on the aromatic rings[4i,j,10,12] but also on the bridging positions,[4d,j] allowing the construction of polyfunctionalized host molecules.

Compared to conventional calixarenes,[15] one of the other salient features of heterocalixaromatics is the incorporation of various heteroaromatic rings. The combination of bridging heteroatoms and heteroaromatic rings has resulted indeed in a few useful macrocyclic hosts in supramolecular chemistry. Due to the conjugative electron-donating effect of the bridging nitrogen atoms, azacalix[*n*]pyridines, for instance, are able to strongly and selectively complex with metal ions[4c,h] and neutral molecular guests[4e] including fullerenes,[4a,b,f,g] while oxacalix[2]arene[2]triazines provide a unique electron-deficient cleft to accommodate a halide anion.[16] On the other hand, NH-bridged calix[2]arene[2]triazines[10a] and oxacalix[2]arene[2]pyrazine[17] have been found to undergo, respectively, hydrogen-bond-directed and silver-coordination-driven molecular self-assembly. As a continuation of our interest in exploring supramolecular chemistry of novel and functional heterocalixaromatics, we report herein the highly efficient synthesis and selective bromination of azacalix[4]pyrimidines.

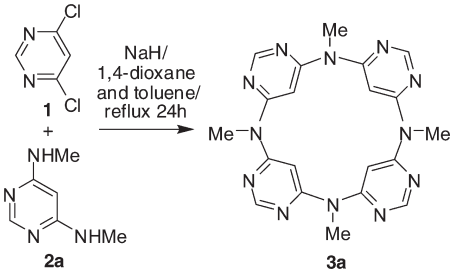
Pyrimidine is a useful ligand in coordination chemistry. It has also been used recently by Katz[11c] and by Dehaen[12] for the construction of oxygen- and sulfur-bridged calix[2]arene[2]pyrimidines. To enhance the ability of pyrimidine nitrogen atoms to coordinate metal ions and to form hydrogen bonding with hydrogen bond donors, however, it is essential to introduce electron-donating groups such as an amino group onto 4- and 6-positions. We therefore envisioned that azacalix[4]pyrimidines would provide a new type of polyfunctionalized macrocyclic host molecules in supramolecular chemistry.

Results and Discussion

We initially attempted the synthesis of methylazacalix[4]pyrimidine **3a** from a straightforward cyclic condensation reaction between 4,6-dichloropyrimidine **1** and 4,6-bis(methylamino)pyrimidine **2a** (Table S1 in the Supporting Information). In the presence of sodium hydride as a base, the reaction of **1** and **2a** in a mixture of 1,4-dioxane and toluene solution proceeded smoothly to give desired methylazacalix[4]pyrimidine **3a** and a mixture of inseparable oligomers. As summarized in Table 1, a large excess amount of sodium hydride was necessary to effect the condensation reaction (entries 1 and 2, Table 1), and use of too many folds of base, however, did not further improve the chemical yield of the macrocyclic product (entries 3 and 4, Table 1). Although the formation of azacalix[4]pyrimidine did not require reaction in a highly dilute concentration, a substrate concentration around 0.067 M (2 mmol substrate in 30 mL of solvent) appeared beneficial (entries 2, 5, and 6, Table 1). A mixture of 1,4-dioxane and toluene (1:1) as the solvent worked better than a single organic solvent such as 1,4-dioxane and toluene (entries 2, 7, and 8, Table 1).

Under the optimized conditions, macrocyclic condensation reaction between **1** and other 4,6-bis(amino)pyrimidines

TABLE 1. Synthesis of 3a from a Straightforward Macrocyclic Condensation Reaction between 1 and 2a



entry	NaH (equiv)	1,4-dioxane/ toluene (v/v)	substrate concn (mM)	**3a** (%)[a]
1	6.3	1:1	66.7	22
2	8.3	1:1	66.7	35
3	10.4	1:1	66.7	33
4	12.5	1:1	66.7	34
5	8.3	1:1	133.4	26
6	8.3	1:1	33.3	27
7	8.3	1:0	66.7	32
8	8.3	0:1	66.7	0[b]

[a]Isolated yield. [b]Only dimer was obtained in 29%.

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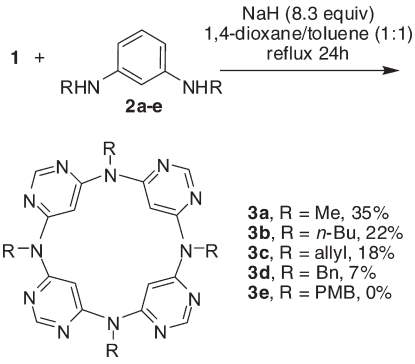
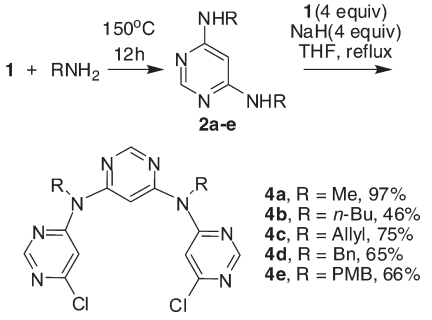
SCHEME 1. Synthesis of Azacalix[4]pyrimidines 3 from Reaction between 1 and 2



SCHEME 2. Synthesis of Dichlorinated Linear Trimers 4

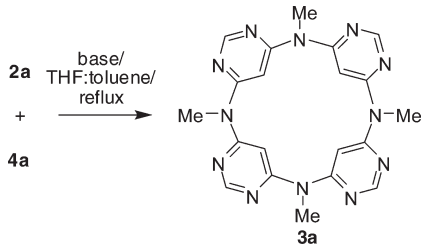


2b−**e** was performed. Unfortunately, the desired products **3b**−**d** were obtained in very low yields (7−22%). As an extreme case, reaction of 4,6-dichloropyrimidine **1** with 4,6-bis(*para*-methoxybenzylamino)pyrimidine **2e** did not give any macrocyclic product **3e** at all (Scheme 1).

In order to improve the synthetic efficiency and also to establish the method for the preparation of differently N-substituted azacalix[4]pyrimidine derivatives, we then studied the 1 + 3 macrocyclic cross-coupling reaction between **2a** and dichlorinated linear trimer **4a**. The latter reactant **4a** was conveniently prepared from the aromatic nucleophilic substitution reaction of **2a** with 4 equiv of **1** (Scheme 2). The optimization results for the reaction of **2a** with **4a** are tabulated in Table 2. It was obvious that bases such as K_2CO_3, KOBu^t, NaOH, and NaOBu^t did not promote the reaction effectively, giving either no product or a very low yield of the product (entries 1−4, Table 2). Fortunately, the use of NaH as a base afforded desired macrocyclic product **3a**. The chemical yield of **3a** was, however, governed strongly by the solvent used. In tetrahydrofuran (THF), for example, the chemical yield of **3a** ranged from 34 to 51% (entries 5−7, Table 2), while a very low yield (14%) of **3a** was observed in toluene (entry 13, Table 2). In a mixture of THF and toluene with the volume ratio of 1:5 to 5:1, good yields (52−70%) of the product were obtained (entries 8−12, Table 2). It was also notable that the substrate concentration affected the efficiency of the formation of the product (entries 6, 9, and 10, Table 2). The highest chemical yield (70%) of **3a** was obtained when the substrate concentration of 5.6 mM was employed (entry 9, Table 2).

Applying the optimized conditions for the synthesis of **3a** (entry 9, Table 2), the reaction of 4,6-bis(amino)pyrimidine

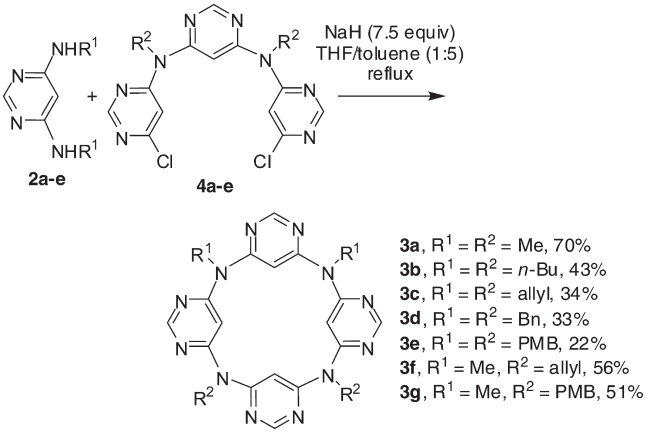
TABLE 2. Synthesis of 3a from a 3 + 1 Macrocyclic Fragment Coupling Reaction of 2a with 4a



entry	base (equiv)	THF/ toluene (v/v)	substrate concn (mM)	time (h)	**3a** (%)[a]
1	K_2CO_3 (3.5)	1:0	66.7	24	0
2	KOBu^t (3.5)	1:0	66.7	24	0
3	NaOH (3.5)	1:0	66.7	24	5
4	NaOBu^t(3.5)	1:0	66.7	24	26
5	NaH (3.5)	1:0	66.7	6	51
6	NaH (7.5)	1:0	66.7	6	40
7	NaH (7.5)	1:0	5.6	6	34
8	NaH (7.5)	1:1	5.6	6	54
9	NaH (7.5)	1:5	5.6	6	70
10	NaH (7.5)	1:5	2.8	6	52
11	NaH (7.5)	1:8	5.6	8	56
12	NaH (7.5)	5:1	5.6	6	52
13	NaH (7.5)	0:1	5.6	72	14

[a]Isolated yield.

SCHEME 3. Synthesis of Azacalix[4]pyrimidines 3 from Reaction between 2 and 4



derivatives **2a**−**e** with other linear trimers **4b**−**e**, which were prepared from **2a**−**e** and 4,6-dichloropyrimidine **1** (Scheme 2), afforded the corresponding azacalix[4]pyrimidine derivatives **3b**−**g** (Scheme 3). Almost all reactions gave moderate to good chemical yields. In the case of *N*-PMB-substituted azacalix-[4]pyrimidine **3e**, a slightly low chemical yield (22%) was obtained owing to the cleavage of *para*-methoxybenzyl group(s) from the reactants and product under the reaction conditions. This was evidenced by the isolation of *para*-methoxybenzaldehyde from the reaction mixture. It was worth noting that the 1 + 3 fragment coupling approach, which was different from the direct condensation reaction of **1** with **2** (Scheme 1), allowed us to prepare azacalix[4]pyrimidines bearing different substituents on the nitrogen bridges. For example, azacalix[4]pyrimidines **3f** and **3g**, which contained methyl and allyl, and methyl and PMB,

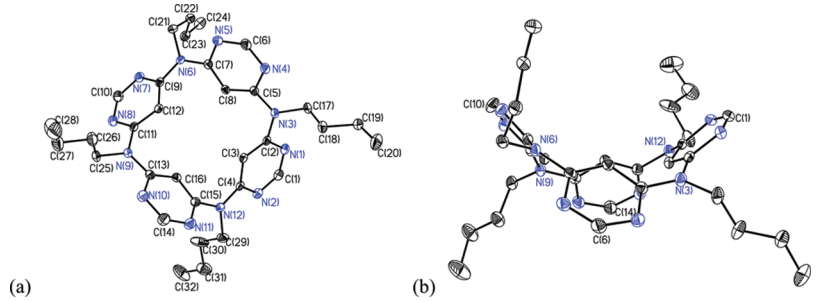


FIGURE 1. X-ray crystal structure of **3b**: (a) top view and (b) side view. All hydrogen atoms and the disorders of C(18), C(19), and C(20) are omitted for clarity. Selected bond lengths (Å): C(2)−N(3) 1.409, N(3)−C(5) 1.382, C(7)−N(6) 1.405, N(6)−C(9) 1.379, C(11)−N(9) 1.413, N(9)−C(13) 1.377, C(4)−N(12) 1.369, N(12)−C(15) 1.407. Selected interatomic distances (Å): C(1)−C(10) 8.288; C(6)−C(14) 8.191.

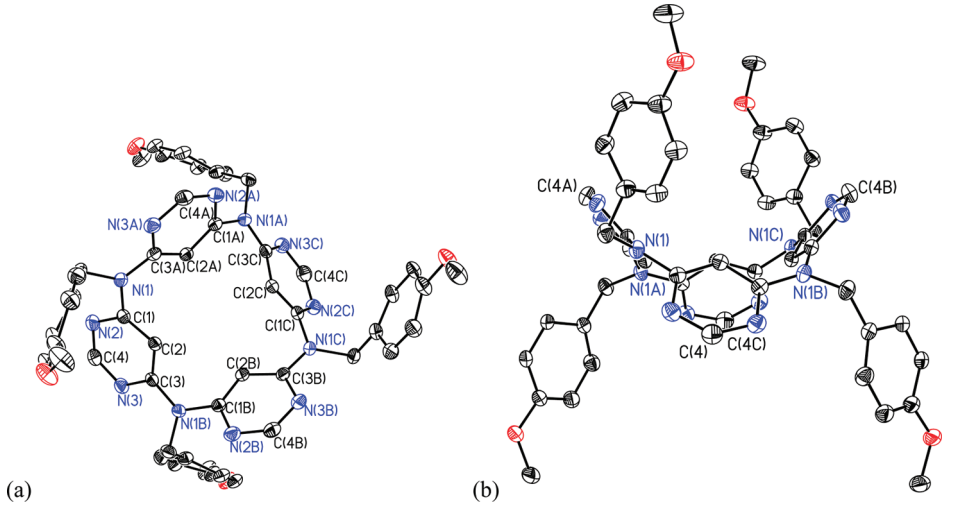


FIGURE 2. X-ray crystal structure of **3e**: (a) top view and (b) side view. All hydrogen atoms and the disorders of **3e** are omitted for clarity. Selected bond lengths (Å): C(1)−N(1) 1.415, N(1)−C(3) 1.374, C(1A)−N(1A) 1.415, N(1A)−C(3C) 1.374, C(1C)−N(1C) 1.415, N(1C)−C(3B) 1.374, C(1B)−N(1B) 1.415, N(1B)−C(3) 1.374. Selected interatomic distances (Å): C(4)−C(4C) 7.931; C(4A)−C(4B) 7.931.

respectively, were synthesized in good yields from the reaction of **2a** with **4c** and with **4e** (Scheme 3).

The structures of all products were established on the basis of spectroscopic data, microananlysis (see Supporting Information), and single-crystal X-ray diffraction analysis (Supporting Information, Table S1). The conformational structures of azacalix[4]pyrimidines warrant addressing. As illustrated in Figures 1 and 2, azacalix[4]pyrimidines **3b** and **3e** adopted twisted 1,3-alternate conformation in the solid state. Judging from the bond lengths and angles, we found that each of the bridging nitrogen atoms was sp^2 electron-configured and formed conjugation with one of its neighboring pyrimidine rings. Due to the different steric effect between *n*-butyl and *para*-methoxybenzyl, the cavity of **3b** and **3e** was varied. The upper-rim distance of **3b** was in the range of 8.191 to 8.288 Å, while that of **3e** was 7.931 Å (see captions of Figures 1 and 2). It was also interesting to note that two molecules of **3e** self-assembled into a spherical dimeric structure, which further allied into channels in the solid state (Figure 3).

It was important to note that all macrocyclic products **3** gave very simple ^{1}H and ^{13}C NMR spectra (see Supporting Information), indicating symmetrical structure in solution. It was most likely that azacalix[4]pyrimidines **3** are very fluxional in solution, and the rates of interconversion of various conformational structures might be very rapid relative to the NMR time scale. The high conformational mobility of these macrocycles was 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 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.

To functionalize the resulting azacalix[4]pyrimidine derivatives, bromination reaction was investigated preliminarily. Being substituted by two amino groups, the pyrimidine ring in macrocycle **3a** was ready to undergo regiospecific electrophilic bromination reaction at the 5-position, giving the lower-rim brominated products (Scheme 4). To our delight, the degree of bromination was nicely and conveniently controlled by varying the ratio of halogenating reagents NBS and by controlling the reaction temperature (Table 3). For example, the use of 1.2 equiv of NBS in chloroform at room temperature gave monobrominated product **5** in a moderate yield (entry 1, Table 3). The use of acetic acid as the solvent instead of

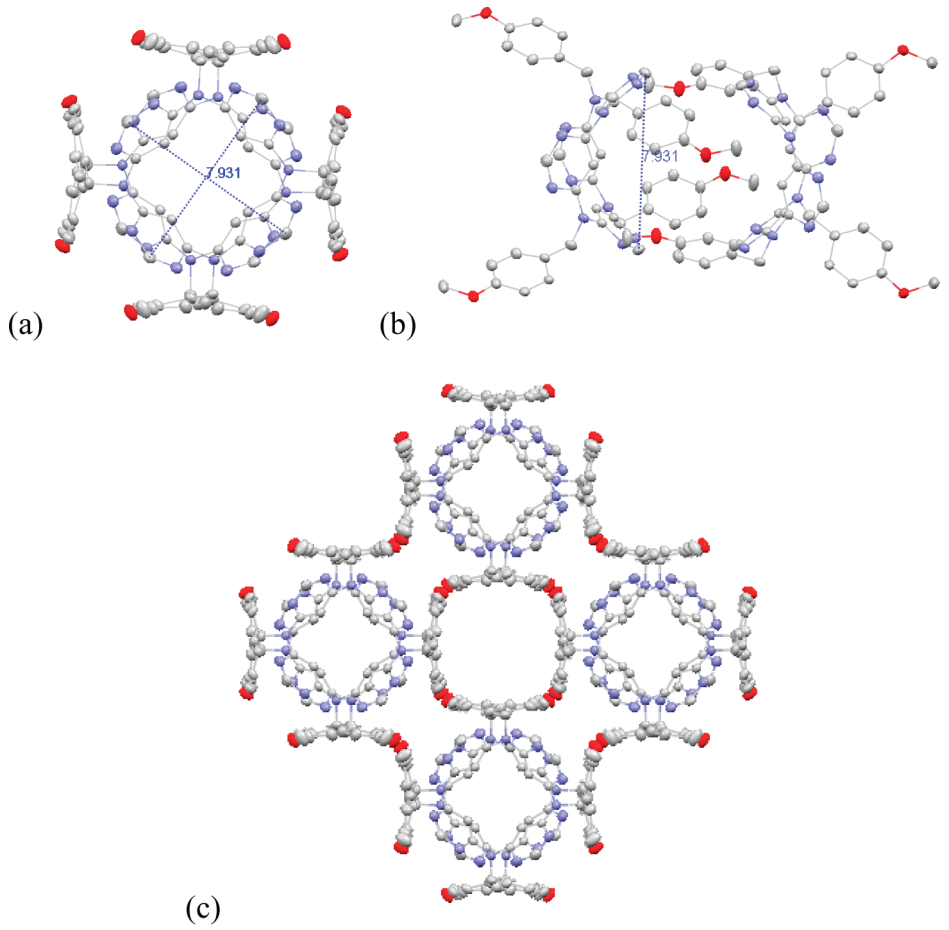


FIGURE 3. Spherical dimeric structure of **3e** along the *c*-axis (a) and *b*-axis (b), and a packing diagram of **3e** along the *c*-axis (c).

SCHEME 4. Selective Bromination of Azacalix[4]pyrimidine 3a

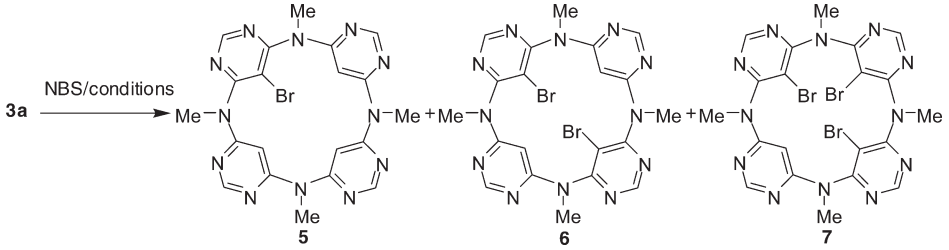


TABLE 3. Selective Bromination of Azacalix[4]pyrimidine 3a

entry	NBS (equiv)	solvent	*T* (°C)	time (h)	Product (%)[a]
1	1.2	$CHCl_3$	rt	24	**5** (41)
2	1.2	CH_3CO_2H	rt	12	**5** (85)[b]
3	2.5	$CHCl_3$	70	12	**6** (84)
4	2.5	CH_3CO_2H	70	4	**6** (85)[c]
5	6.0	CH_3CO_2H	reflux	20	**7** (58)[d]

[a]Isolated yield. [b]A trace amount of **6** was observed. [c]A trace amount of **7** was observed. [d]A trace amount of **5** and **6** was observed.

chloroform facilitated the reaction and improved the chemical yield of **5** to 85% (entry 2, Table 3). When 2.5 equiv of NBS was employed and the reaction carried out in chloroform at 70 °C, dibrominated product **6** was isolated as the major product in 84% (entry 3, Table 3). Change of solvent from chloroform to acetic acid resulted in the rapid formation of 1,3-dibrominated product **6** as nearly the sole product in 85% yield in 4 h (entry 4, Table 3). Further increase of the amount of NBS used and of the reaction temperature gave rise to the formation of tribrominated product. This was exemplified by the isolation of tribrominated product **7** as the major product when **3a** was refluxed with 6 equiv of NBS in acetic acid for 20 h (entry 5, Table 3). It should be noted that no fully brominated product was observed under all forcing conditions tried. The selective formation of 1,3-dibrominated product **6** and no formation of fully brominated product implied that the steric factor may play a decisive role in the selective electrophilic bromination reaction. As revealed by single-crystal X-ray diffraction analysis (Table S1, Supporting Information), while dibromo-substituted azacalix[4]pyrimidine product **6** adopted a highly symmetrical 1,3-alternate conformation (Figure 4), slightly twisted

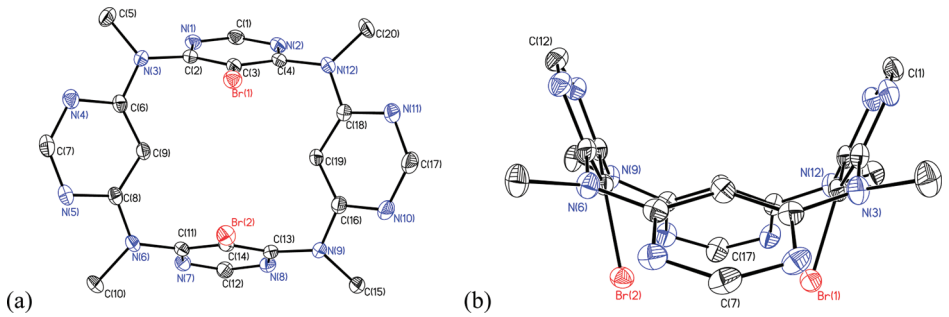


FIGURE 4. X-ray crystal structure of **6**: (a) top view and (b) side view. All hydrogen atoms are omitted for clarity.

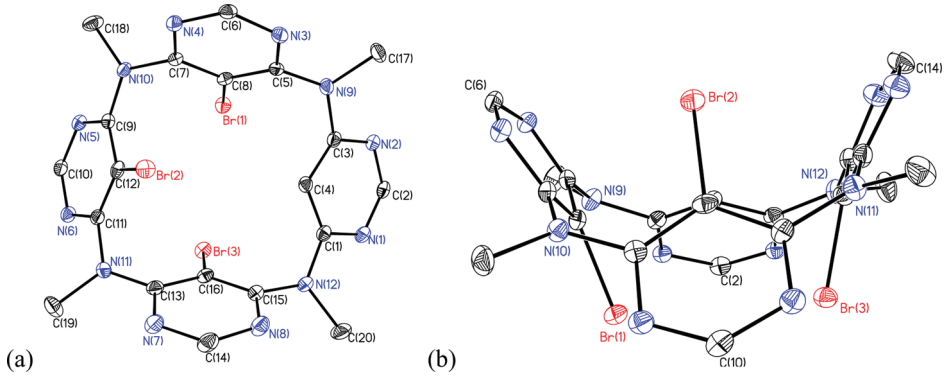


FIGURE 5. X-ray crystal structure of **7**: (a) top view and (b) side view. All hydrogen atoms are omitted for clarity.

1,3-alternate conformational structures were observed for product **7** in the solid state (Figure 5).

Conclusion

In summary, we have developed two synthetic approaches to azacalix[4]pyrimidines. While macrocyclic condensation reaction between 4,6-dichloropyrimidine and 4,6-bis(alkylamino)-pyrimidines generally suffered from low yields, an efficient 1+3 macrocyclic fragment coupling reaction afforded azacalix-[4]pyrimidines in the yield ranging from 22 to 70%. Being substituted by two amino groups, the pyrimidine ring in the macrocycle was ready to undergo regiospecific electrophilic bromination reaction at the 5-position. Simply by controlling the reaction temperature and the ratio of NBS, selective low-rim bromination reaction was accomplished, producing mono-, di-, and tribrominated products in good yields. The easy availability of azacalix[4]pyrimidines would render these novel multi-nitrogen-containing macrocycles useful in molecular recognition and supramolecular assembly. The selectively brominated azacalix-[4]pyrimidine derivatives, on the other hand, would provide unique building blocks for the construction of high-level molecular architectures by taking advantage of flourishing metal-catalyzed cross-coupling reaction protocols.

Experimental Section

General Procedure for the Synthesis of Azacalix[4]pyrimidines 3a−d from a Straightforward Macrocyclic Condensation Reaction between 1 and 2a−d. To a solution of **2a−d** (2 mmol) in dry solvents (30 mL) at room temperature was added NaH (200 mg, 8.3 mmol) slowly, and the mixture was heated to reflux. After 12 h, **1** (2 mmol) was added to the mixture slowly and the reaction mixture was refluxed for another 24 h, then cooled to room temperature and a small amount of water was slowly added. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (200 mL). The organic solution was washed with brine (3 × 50 mL) and dried over with anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (100−200) with a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure products **3a−d**.

General Procedure for the Synthesis of Azacalix[4]pyrimidines 3a−g from 2a−e and 4a−e by 1 + 3 Fragment Coupling Reaction. To a solution of **2a−e** (1 mmol) in dry THF (30 mL) at room temperature was added NaH (180 mg, 7.5 mmol) slowly, and the mixture was heated to reflux. After 12 h, the dry toluene (150 mL) and **4a−e** (1 mmol) were added to the mixture, and the reaction mixture was refluxed for another several hours, then cooled to room temperature and a small amount of water was slowly added. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (200 mL). The organic solution was washed with brine (3 × 50 mL) and dried over with anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (100−200) with a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure products **3a−g**.

Selective Monobromination of 3a To Prepare Compound 5. A mixture of **3a** (107 mg, 0.25 mmol) and NBS (53.4 mg, 0.3 mmol) in HOAc (or $CHCl_3$) (10 mL) at room temperature was stirred. After 12 h, the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (50 mL). The organic solution was washed with aqueous KOH solution (2 M) and dried over with anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (200−300) with a mixture of dichloromethane and acetone as the mobile phase to give pure **5** (108 mg, 85%) as a white solid. If the solvent was $CHCl_3$, the reaction rate was very slow. After 24 h, the pure product was 52 mg, 41%: mp >300 °C; IR (KBr) ν 1589, 1526, 1481, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81

(s, 1H), 8.76 (d, J = 0.9 Hz, 1H), 8.72 (d, J = 0.8 Hz, 2H), 7.04 (d, J = 0.9 Hz, 1H), 6.19 (d, J = 0.9 Hz, 2H), 3.63 (s, 6H), 3.56 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.64, 162.59, 162.1, 161.8, 160.1, 159.3, 158.1, 107.6, 101.5, 96.1, 37.1, 35.9; MS (EI) m/z (%) 508 $[M + 2]^+$ (38), 506 $[M]^+$ (40), 427 $[M - Br]^+$ (100). Anal. Calcd for $C_{20}H_{19}N_{12}Br$: C, 47.35; H, 3.77; N, 33.13. Found: C, 46.95; H, 3.56; N, 32.83.

Selective Dibromination of 3a To Prepare Compound 6. A mixture of **3a** (107 mg, 0.25 mmol) and NBS (111 mg, 0.625 mmol) in HOAc (or $CHCl_3$) (10 mL) was heated to 70 °C. After 4 h, the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (50 mL). The organic solution was washed with aqueous KOH solution (2 M) and dried over with anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on a silica gel column (200−300) with a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure **6** (125 mg, 85%) as a white solid. If the solvent was $CHCl_3$, the reaction rate was much slower. After 12 h, the pure product (123 mg, 84%) was obtained: mp 287−288 °C; IR (KBr) ν 1588, 1546, 1475, 1427, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 2H), 8.70 (s, 2H), 5.25 (s, 2H), 3.57 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.0, 158.9, 158.4, 111.5, 93.3, 36.9; MS (EI) m/z (%) 588 $[M + 4]^+$ (44), 586 $[M + 2]^+$ (100), 584 $[M]^+$ (46), 507 $[M - Br + 2]^+$ (43), 505 $[M - Br]^+$ (45), 425 $[M - 2Br]^+$ (32). Anal. Calcd for $C_{20}H_{18}N_{12}Br_2$: C, 40.97; H, 3.09; N, 28.67. Found: C, 40.86; H, 3.11; N, 28.21.

Selective Tribromination of 3a To Prepare Compound 7. A mixture of **3a** (107 mg, 0.25 mmol) and NBS (267 mg, 1.5 mmol) in HOAc (10 mL) was refluxed for 20 h. After workup as that for **6**, product **7** was obtained (96 mg, 58%) as a white solid: mp > 300 °C; IR (KBr) ν 1587, 1556, 1510, 1473, 1426 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.75 (s, 2H), 8.71 (s, 1H), 5.86 (d, J = 0.8 Hz, 1H), 3.67 (s, 6H), 3.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 163.1, 162.48, 162.45, 158.6, 157.1, 106.4, 100.4, 96.5, 39.1, 38.1; MS (EI) m/z (%) 668 $[M + 6]^+$ (6), 666 $[M + 4]^+$ (20), 664 $[M + 2]^+$ (21), 662 $[M]^+$ (7), 587 $[M - Br + 4]^+$ (37), 585 $[M - Br + 2]^+$ (100), 583 $[M - Br]^+$ (43), 505 $[M - 2Br + 2]^+$ (8), 503 $[M - 2Br]^+$ (5), 425 $[M - 3Br]^+$ (12). Anal. Calcd for $C_{20}H_{19}N_{12}Br_3$: C, 36.11; H, 2.58; N, 25.27. Found: C, 36.26; H, 2.65; N, 24.98.

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Supporting Information Available: Experimental details, full characterization of products, ^{1}H and ^{13}C NMR of the products, X-ray molecular structure of **3b**, **3e**, **6**, and **7** (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.