JOC The Journal of Organic Chemistry

Article

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Selective Formylation of Azacalixpyridine Macrocycles and Their Transformation to Molecular Semicages

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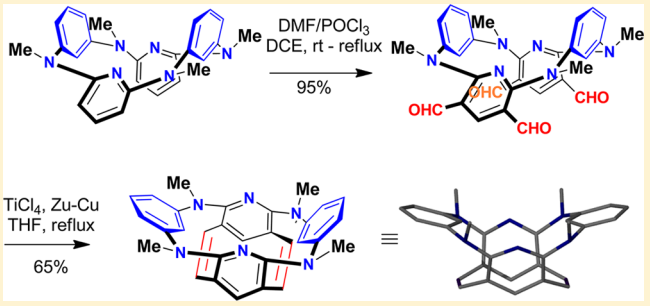
Supporting Information

ABSTRACT: The aromatic electrophilic formylation reaction of azacalix[2]arene[2]pyridine and azacalix[4]pyridine were systematically studied. By simply controlling the ratio of reactants and the reaction temperature, the Vilsmeier−Haack reaction selectively afforded mono-, di-, and tetra-formylated azacalix[2]arene[2]pyridines and azacalix[4]pyridines. The preferential and selective functionalization reactions of macrocycles were discussed in terms of their conformational structure and conjugation effect between aromatic subunits and bridging nitrogen atoms. All resulting functionalized azacalix[2]arene[2]pyridines and azacalix[4]pyridines adopted a 1,3-alternate conformation both in the crystalline state and in solution. Taking advantage of the close proximity of aldehyde groups in 1,3-alternate di- and tetra-formylated azacalixpyridine macrocycles, the McMurry reductive coupling reaction of carbonyls was accomplished to yield unique semicage molecules.



INTRODUCTION

Heteracalixaromatics, or heteroatom-bridged calix(het)arenes, are unique and powerful synthetic host molecules in macrocyclic and supramolecular chemistry.[1−4] In comparison to conventional calixarenes, introduction of heteroatoms into the linking positions between arene units results in macrocycles with tunable conformations and electronic properties because the heteroatoms can adopt different electronic configurations and form varied conjugation systems with their adjacent aromatic rings.[5−10] The combination of different heteroatoms and various heterocyclic aromatic rings therefore generates not only diverse heteracalixaromatic compounds but also functional macrocycles that are versatile in molecular recognition and self-assembly.[11,12] Application of heteracalixaromatics has now widely spread from the recognition and sensing of a large number of cations,[1] anions[1,13] and electron neutral molecules,[1,14] including fullerenes[1,15] to the preparation of organic metal frameworks[16] and organosilver clusters,[17] the construction of liquid crystals[18] and stimuli-responsive vesicles,[19] and the fabrication of CO_2 absorbents[20] and HPLC stationary phases.[21]

As an important and useful member of heteracalixaromatics, azacalixpyridines are synthesized by means of the fragment coupling approach.[7,8] Starting from 2,6-aminopyridines as dinucleophiles and 2,6-dihalopyridines as dielectrophiles, the stepwise aromatic nucleophilic substitution reaction and Pd-catalyzed cross-coupling reaction led to the formation of azacalix[n]pyridines (n = 4−10).[1] Employment of other appropriate reaction counterparts, the fragment coupling strategy enables the synthesis of azacalixpyridine macrocycles that incorporate aromatic rings other than the pyridine unit.[1] Although the methods for the construction of parent azacalixpyridine macrocyclic rings have been established and well-developed, further functionalization of this type of macrocycle remains largely unexplored. For example, copper(II)-catalyzed and -mediated arene C−H bond transformations of azacalix[1]arene[3]pyridines through arylcopper(II) and arylcopper(III) intermediates have provided a powerful means to install various functional groups regiospecifically on the lower-rim position of the benzene unit of the macrocycles[22] (Figure 1). Very recently, a one-pot [2 + 2 + 2] fragment coupling reaction has been shown to efficiently produce azacalix[3]pyridine[3]pyrimidines with functional groups on the linking nitrogen atoms[15a] (Figure 1). However, direct functionalization on the pyridine nucleus is not yet known. For the applications of azacalixpyridines in host−guest chemistry

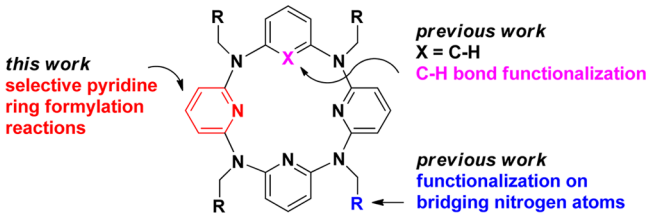


Figure 1. Different methods for the preparation of functionalized azacalixpyridine macrocycles.

Received: July 25, 2015
Published: August 24, 2015

DOI: 10.1021/acs.joc.5b01722
J. Org. Chem. 2015, 80, 9272−9278

and in the construction of high-level and sophisticated molecular and supramolecular architectures to be explored further, azacalixpyridine macrocycles that bear functional groups on pyridine subunits are highly desirable.

The study on direct chemical manipulations of pyridine rings incorporated in azacalixpyridine compounds is most likely hampered by the basic knowledge of pyridine having lower reactivity than benzene. Electrophilic aromatic substitution reactions of a pyridine generally require harsh reaction conditions. However, careful scrutiny of the structure of azacalix[4]pyridine reveals that all bridging nitrogen atoms form conjugation with their neighboring pyridines. In the case of azacalix[2]arene[2]pyridine, each pyridine ring conjugates strongly with both nitrogen atoms at the 2,6-positions.[7,8] As a consequence, electron density of pyridine rings in azacalixpyridine macrocycles is increased. We envisioned therefore that pyridine rings would be amenable to electrophilic aromatic substitution reactions under relatively mild conditions. To our delight, azacalixpyridines were able to undergo selective formylation reactions to afford mono- to multiformylated macrocyclic products (Figure 1). Further elaboration of di- and tetra-formylated azacalixpyridines under McMurry reaction conditions furnished open-box (semicage) molecules. We report herein the details of our study.

RESULTS AND DISCUSSION

Because the aldehyde functional group is extremely useful in organic synthesis as it is readily transformable to other diverse functional groups,[23] we concentrated our effect on the introduction of formyl group(s) into the azacalixpyridine macrocycles. Among many documented methods for the formation of a formyl group, the Vilsmeier–Haack reaction[24] was chosen because of the easy availability and high electrophilic reactivity of the Vilsmeier reagent.

We initiated our study with the examination of selective formylation of azacalix[2]arene[2]pyridine **1**. As illustrated in Figure 2, the reaction of azacalix[2]arene[2]pyridine **1** with 1.5 equiv of the Vilsmeier reagent at 0 °C to room temperature in 1,2-dichloroethane (DCE) yielded, after workup, monoformylated azacalix[2]arene[2]pyridine **2** in 50% along with a trace amount of diformylated compounds. With the increase of the Vilsmeier reagent to 8 equiv, efficient diformylation reaction proceeded dominantly. A total chemical yield of 95% was obtained for diformylation products **3** and **4** with the ratio of *syn* to *anti* regioisomers being 1.5 to 1. At an elevated reflux temperature, the reaction of macrocycle **1**, with an excess amount of the Vilsmeier reagent (16 equiv), produced exclusively tetraformylated azacalix[2]arene[2]pyridine **5** in excellent yield. It is important to point out that all formylation reactions occurred site-specifically on pyridine nuclei, and no formylation products on benzene ring(s) were observed. The outcome, which was not surprising or unexpected, is in agreement with the structural features and electronic characteristics of 1,3-alternate azacalix[2]arene[2]pyridine in which pyridine is strongly conjugated with its adjacent amino groups, whereas the benzene ring is nearly perpendicular to the plane defined by bridging nitrogen atoms.[7] In fact, when we performed the Vilsmeier–Haack reaction of an acyclic reactant, namely N^1,N^3-dimethyl-N^1,N^3-di(pyridin-2-yl)benzene-1,3-diamine, under identical conditions, no reaction was observed, implying the necessity and uniqueness of the macrocyclic structure for the reaction. It is also worth addressing that each pyridine ring in macrocycle **1** was able to undergo consecutive

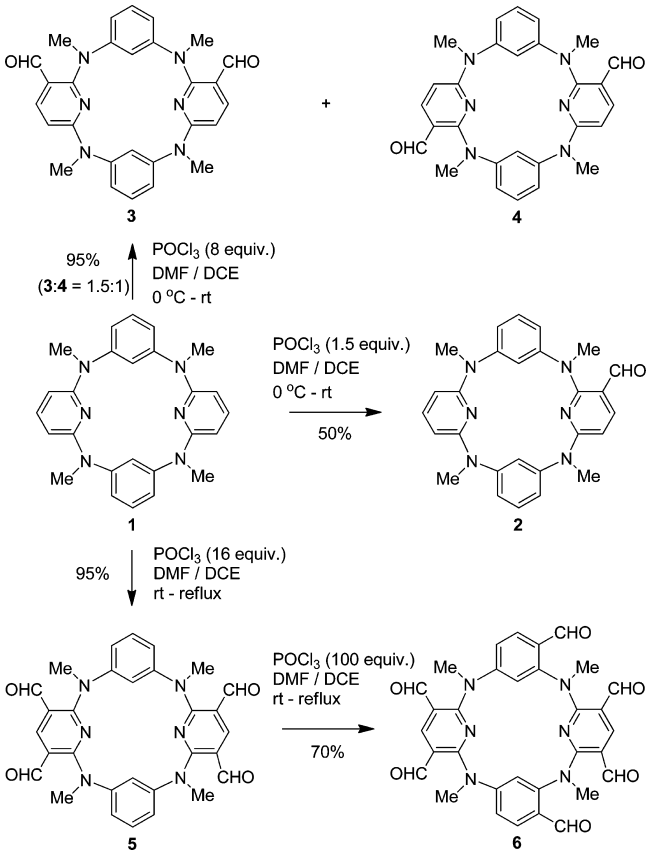


Figure 2. Selective reactions of azacalix[2]arene[2]pyridine **1** with the Vilsmeier reagent.

diformylation reactions with the Vilsmeier reagent. Bearing in mind that the Vilsmeier–Haack reaction proceeds through an iminium salt intermediate,[24] easy reaction of the resulting iminium salt of pyridine with another equiv of the Vilsmeier reagent reflected the high electron density of theiminium-bearing 2,6-diaminopyridine segment. The conjugational electron-donation effect of 2,5-diamino moieties must therefore override the electron-withdrawing effect of one iminium functional group on the pyridine ring, rendering the pyridine ring of 2,6-(diaminopyridin-3-yl)methylene)-*N*-methylmethanaminium intermediate still electrophilic toward the Vilsmeier reagent (Figure 3).

For the benzene ring of **1** to be formylated, the one-pot Vilsmeier–Haack reaction using a very large excess amount of formylating reagent and high reaction temperatures were tested. No desired products were obtained under these forceful

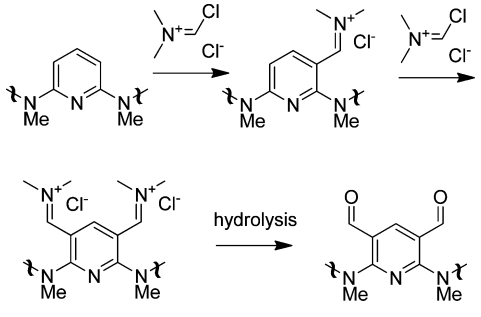


Figure 3. Consecutive diformylation of the 2,6-diaminopyridine moiety.

DOI: 10.1021/acs.joc.5b01722
J. Org. Chem. 2015, 80, 9272–9278

circumstances. Interestingly, when isolated tetraformyl-substituted azacalix[2]arene[2]pyridine **5** was allowed to react with the Vilsmeier reagent in refluxing DCE, formylation did occur on the benzene ring to afford *syn* diformylated product **6** in 70% yield (Figure 2). Only a very trace amount of *anti* diformylated macrocycle was detected. The result suggested that iminium displays a stronger deactivation effect than aldehyde on the benzene moiety. Alternatively, because of the steric effect of two formyl groups on the pyridine ring, the bridging nitrogen atoms in **5** can now probably form more or less conjugation with benzene ring, increasing the electrophilicity of benzene ring. Similar to the formylation reaction of **1**, which gave preferentially *syn* diformylated product **3**, the pronounced selectivity for formation of *syn* diformylated product **6** from the formylation reaction of **5** remains unknown. It could be originated from a conformational change to an energetically favored macrocyclic conformer that enables the formation of a subtle conjugation system, leading to the increase of electron density of the *syn* carbon atoms of two distal benzene rings during the reaction process. Further formylation of compound **6** was not successful, as the monoformylated benzene ring appeared inert to the Vilsmeier reagent even the reaction was conducted at high temperature in a sealed reaction vial.

Azacalix[4]pyridine **7** was also able to undergo the Vilsmeier–Haack reaction. The regioselectivity, however, was not as good as the reaction of its azacalix[2]arene[2]pyridine **1** analogue. For example, under identical conditions, azacalix[4]-pyridine **7** reacted with one equiv of Vilsmeier reagent to produce a mixture of monoformylated product **8** and *syn* and *anti* diformylated products **9** and **10** in 20, 15, and 10% yields, respectively. Employment of two equiv of the Vilsmeier reagent in the reaction resulted in the formation of products **9** and **10** in 25 and 14% yields, respectively (Figure 4). In an attempt to synthesize multiformylated azacalix[4]pyridine macrocycles by means of using a large excess amount of the Vilsmeier reagent in refluxing DCE, we found that the starting material was consumed rapidly. The reaction furnished the formation of at least three major isomers, **11**, **12**, and **13**, in a total chemical yield of 61%. Pure product **11** was isolated in 10% yield after silica gel column chromatography, whereas the other two compounds were hard to separate into their pure forms due to their nearly identical polarities.

It is very interesting to note that, in stark contrast to azacalix[2]arene[2]pyridine **1**, the Vilsmeier–Haack reaction of azacalix[4]pyridine **7** under any of the forceful reaction conditions generated products in which the composing pyridine nuclei was only monoformylated. No diformylation on one pyridine ring of **7** was observed at all. This is in accordance to the conformational structure of azacalix[4]pyridine **7**, which is assembled by four identical 2-aminopyridine subunits in a 1,3-alternate manner.[8] In comparison to the conjugation system of the 2,6-diaminopyridine unit in macrocycle **1**,[7] the 2-amino-pyridine segment in macrocycle **7**[8] is less electron-rich. As a consequence, after the first reaction with the Vilsmeier reagent, the resulting iminium-bearing 2-aminopyridine intermediate became inactive toward further electrophilic aromatic substitution reactions. The Vilsmeier–Haack reaction stopped at the monoformylation stage.

The structures of all products were supported by their spectroscopic data and microanalyses. The structures were also determined unambiguously by single crystal X-ray diffraction analysis. As depicted in Figures 5, 6, and 7, all formylated

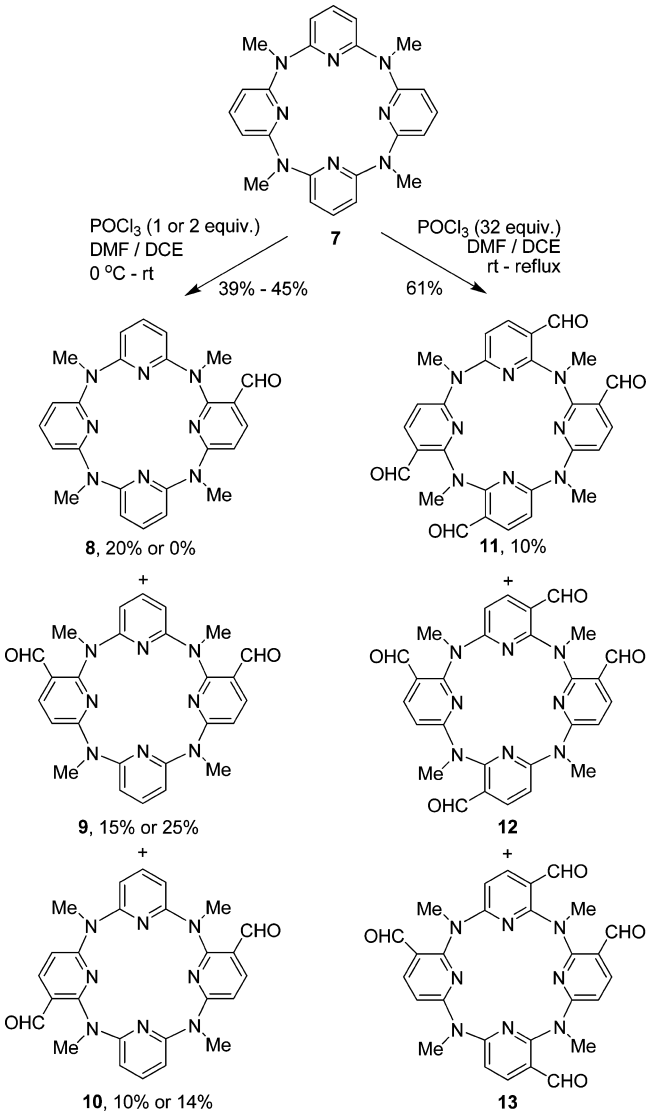


Figure 4. Selective Vilsmeier–Haack reaction of azacalix[4]pyridine **7**.

azacalixpyridine macrocycles adopt a 1,3-alternate conformation in the crystalline state. Although compound **3** showed a slightly distorted 1,3-alternate conformational structure (Figure 5), the tetraformylated azacalix[2]arene[2]pyridine **5** and azacalix[4]pyridine **11** gave highly symmetric macrocyclic conformations (Figures 6 and 7). It was notable that while a pair of distal pyridine rings is orthogonal to the plane defined by all bridging nitrogen atoms, the other pair tends to be procumbent to the plane (Figures 6 and 7). In all cases, bridging nitrogen atoms formed conjugation with the procumbent pyridine rings based on the bond lengths and angles (see Supporting Information). Like their parent azacalix[2]arene[2]pyridine[7] and azacalix[4]pyridine,[8] all resulting functionalized macrocyclic products exhibited one set of proton and carbon signals in their ^{1}H and ^{13}C NMR spectra, respectively, at room temperature. It is indicative of the formation of stable 1,3-alternate conformation[10] in solution for macrocycles that contain multiple formyl groups because steric hindrance prohibited the mobility of the macrocyclic conformation. In the case of monoformylated and diformylated azacalix[2]arene[2]pyridine and azacalix[4]pyridine compounds, however, very fast interconversion of 1,3-alternate

DOI: 10.1021/acs.joc.5b01722
J. Org. Chem. 2015, 80, 9272–9278

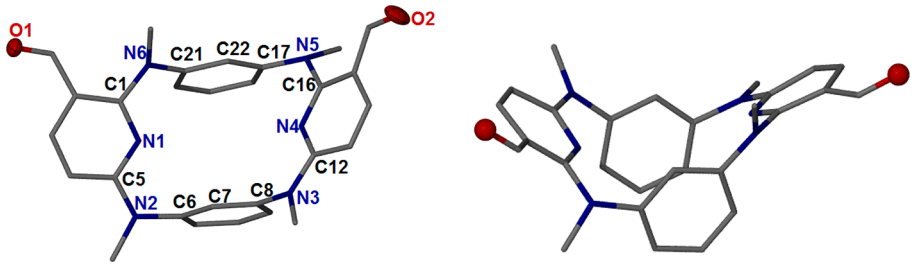


Figure 5. X-ray molecular structure of **3** with top and side views. The molecular structure is depicted in a stick style except for oxygen atoms in an ellipsoid style at 50% probability level.

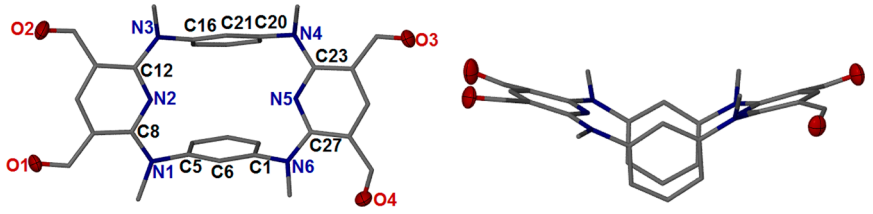


Figure 6. X-ray molecular structure of **5** with top and side views. The molecular structure is depicted in a stick style except for oxygen atoms in an ellipsoid style at 50% probability level.

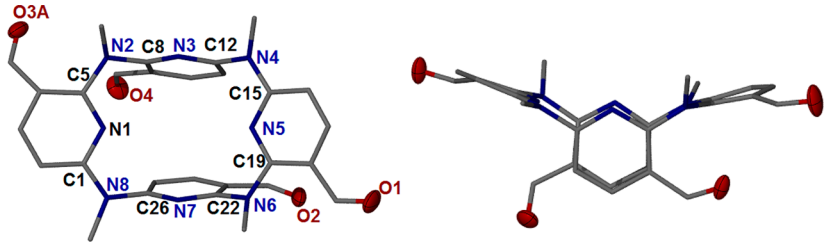


Figure 7. X-ray molecular structure of **11** with top and side views. The molecular structure is depicted in a stick style except for oxygen atoms in an ellipsoid style at 50% probability level.

conformational structures relative to the NMR time scale is responsible for the appearance of one set of resonance signals in the NMR spectra.[10]

Because of the versatile chemical transformability of the aldehyde group,[23] all formyl-containing azacalixpyridines synthesized are valuable, and they provide us with an array of platform molecules for the fabrication of functional and sophisticated molecular structures. To demonstrate their synthetic applications, we undertook the study of the construction of molecular semicages by means of intramolecular McMurry coupling reactions.[25] Because azacalix[2]arene[2]pyridines and azacalix[4]pyridine adopt 1,3-alternate conformation, two formyl-bearing pyridine rings in macrocycles **5** and **9** should be face-to-face paralleled. It brings distal aldehyde groups into proximity in space, enabling the trans-macrocyclic ring coupling of two functional groups. As shown in Figure 8, adopting a standard procedure for the McMurry reductive coupling of carbonyl compounds,[25] azacalix[2]arene[2](3,5-diformylpyridine) **5** and *syn* diformylated azacalix[4]pyridine **9** were transformed smoothly into the corresponding molecular semicages **14** and **15** in good yields. The structures of molecular semicages were established on the basis of spectroscopic data, elemental analysis, and X-ray crystallography. As revealed by a very simple and single set of proton and carbon signals in their respective ^{1}H and ^{13}C NMR spectra, molecules **14** and **15** adopted a highly symmetric structure. This has been further validated by the X-ray single crystal and molecular structures of **14** and **15**, which show

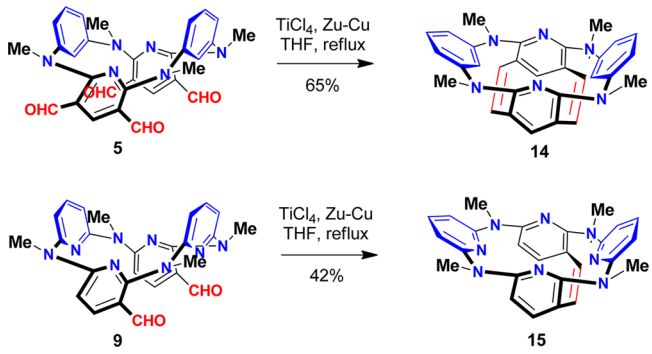


Figure 8. Synthesis of molecular semicages **14** and **15** from intramolecular McMurry reductive coupling reactions of **5** and **9**, respectively.

undoubtedly rigid and symmetric open-box molecules in Figures 9 and 10, respectively. It is worth addressing that the aromatic pyridine rings connected by the vinylene moiety lose their planarity due to the strain of highly rigid semicage structure in the crystalline state (Figure 10).

CONCLUSIONS

In summary, we have achieved the synthesis of functionalized azacalixpyridine macrocycles from the aromatic electrophilic formylation reaction. Under the controlled conditions, the Vilsmeier−Haack reaction afforded selectively mono-, di-, and tetra-formylated azacalix[2]arene[2]pyridines and azacalix[4]-

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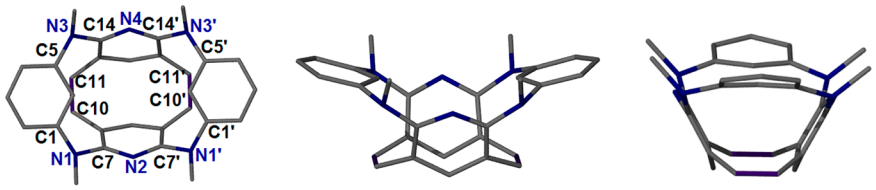

Figure 9. X-ray molecular structure of **14** with top and side views. A solvent molecule was omitted for clarity.

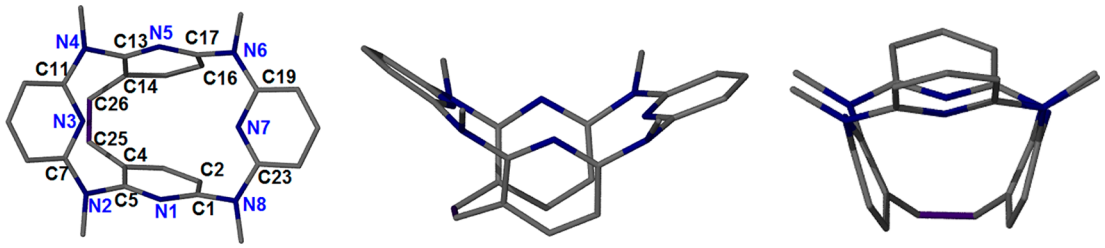

Figure 10. X-ray molecular structure of **15** with top and side views.

pyridines. The preferential functionalization on pyridine rings of azacalix[2]arene[2]pyridine was determined by the structural characteristics of the macrocycle, namely, a 1,3-alternate conformational structure with the formation of strong conjugation of pyridine with its adjacent 2,6-diamino moieties. All resulting functionalized azacalix[2]arene[2]pyridines and azacalix[4]pyridines adopted 1,3-alternate conformation both in the crystalline state and in solution. Taking advantage of the close proximity of aldehyde groups in 1,3-alternate di- and tetra-formylated azacalixpyridine macrocycles, we have accomplished the McMurry reductive coupling reaction of carbonyls and have synthesized successfully unique semicage molecules. Applications of functionalized azacalixpyridine macrocycles are being actively pursued in this laboratory, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Procedure for Selective Formylation of Azacalixpyridine Macrocycles 1 and 7. To 10mL of DMF solution at 0 °C was added dropwise $POCl_3$ (1.5 equiv for the synthesis of **2**; 8 equiv for the synthesis of **3** and **4**; 16 equiv for the synthesis of **5**; 100 equiv for the synthesis of **6**; 1 or 2 equiv for the synthesis of **8**, **9**, and **10**; or 32 equiv for the synthesis of **11**, **12**, and **13**), and the resulting mixture was stirred for 10 min to form the Vilsmeier salt. Then, the Vilsmeier salt was added slowly with a syringe to the solution of reactant **1**, **7**, or **5** (1 mmol) in 60 mL of DCE (60 mL). The reaction mixture was stirred at room temperature (for **2**, **3**, **4**, **8**, **9**, and **10**) or reflux temperature (for **5**, **6**, **11**, **12**, and **13**) until the starting material was completly consumed. The reaction mixture was poured into crushed ice and extracted with CH_2Cl_2 (3 × 50 mL); then, the organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography on a silica gel column using a mixture of dichloromethane and acetone (20:1−10:1) as eluent to give pure product. X-ray quality single crystals **3**, **5**, and **11** were obtained by diffusing hexane into the solutions of **3**, **5**, and **11** in chloroform. Characterization data of all products are listed below.

2. Yellow solid; 225 mg; 50% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.75−6.56 (m, 5H), 6.32 (d, J = 8.7 Hz, 1H), 6.07 (d, J = 7.9 Hz, 2H), 3.34 (s, 1H), 3.26 (s, 1H), 3.20 (s, 1H), 3.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 162.5, 160.2, 158.3, 158.2, 149.5, 149.1, 148.5, 146.7, 141.8, 139.1, 129.5, 129.1, 125.3, 124.5, 123.8, 123.3, 123.2, 119.8, 111.9, 100.1, 96.4, 95.9, 43.4, 39.2, 39.2, 39.1; IR (KBr, cm^{-1}) ν 2873, 1668, 1591, 1574, 1489, 1378, 1234, 1125, 813, 774, 695; HRMS (APCI-ion trap) calcd for $C_{27}H_{27}N_6O$ [M + H]$^+$, 451.2241, found 451.2237; Elemental Anal. Calcd (%) for $C_{27}H_{26}N_6O$ C 71.98, H 5.82, N 18.65; Found C 72.00, H 5.83, N 18.53.

3. Yellow solid; 272 mg; 57% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.12 (t, J = 7.9 Hz, 1H), 6.98 (t, J = 8.3 Hz, 1H), 6.78 (dd, J = 7.9, 1.8 Hz, 2H), 6.69 (s, 1H), 6.66−6.61 (m, 3H), 6.28 (d, J = 8.7 Hz, 2H), 3.36 (s, 3H), 3.28 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 161.8, 159.8, 148.8, 147.3, 142.8, 129.8, 128.9, 126.2, 126.2, 122.1, 121.7, 110.6, 99.0, 44.1, 38.9; IR (KBr, cm^{-1}) ν 2834, 1645, 1600, 1580, 1545, 1489, 1385, 1280, 1243, 1130, 1081, 936, 796, 701, 602, 452; HRMS (APCI-ion trap) calcd for $C_{28}H_{27}N_6O_2$ [M + H]$^+$, 479.2190, found 479.2186; Elemental Anal. Calcd (%) for $C_{28}H_{26}N_6O_2$ C 70.28, H 5.48, N 17.56; Found C 70.13, H 5.83, N 17.48.

4. Yellow solid; 184 mg; 38% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 2H), 8.04 (d, J = 8.7 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 6.72 (d, J = 8.2 Hz, 2H), 6.59 (d, J = 7.8 Hz, 2H), 6.45 (d, J = 8.8 Hz, 2H), 6.38 (s, 2H), 3.28 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 162.5, 160.8, 149.2, 146.1, 140.8, 129.9, 119.4, 119.2, 115.9, 114.8, 102.6, 42.2, 39.6; IR (KBr, cm^{-1}) ν 2829, 2738, 1692, 1666, 1592, 1575, 1543, 1488, 1380, 1258, 1125, 1078, 811, 799, 767, 695, 600; HRMS (APCI-ion trap) calcd for $C_{28}H_{27}N_6O_2$ [M + H]$^+$, 479.2190; found, 479.2185; Elemental Anal. Calcd (%) for $C_{28}H_{26}N_6O_2$ C 70.28, H 5.48, N 17.56; Found C 69.94, H 5.45, N 17.49.

5. Yellow solid; 507 mg; 95% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 4H), 8.37 (s, 2H), 7.11 (t, J = 7.9 Hz, 2H), 6.81 (dd, J = 7.9, 1.9 Hz, 4H), 6.69 (t, J = 1.8 Hz, 2H), 3.35 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 159.0, 153.8, 147.9, 130.1, 125.7, 124.4, 111.5, 44.0; IR (KBr, cm^{-1}) ν 2845, 2723, 1667, 1596, 1574, 1516, 1488, 1393, 1339, 1176, 1129, 1085, 937, 782, 694, 608, 504; HRMS (ACPI-ion trap) calcd for $C_{30}H_{27}N_6O_4$ [M + H]$^+$, 535.2088; found, 535.2083; Elemental Anal. Calcd (%) for $C_{30}H_{26}N_6O_4$ C 67.40, H 4.90, N 15.72; Found C 67.36, H 4.98, N 15.57.

6. Yellow solid; 428 mg; 70% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 2H), 9.85 (s, 2H), 9.67 (s, 2H), 8.43 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 6.81 (s, 2H), 3.38 (s, 6H), 3.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 186.1, 186.0, 158.9, 158.8, 154.1, 153.8, 153.1, 149.1, 132.2, 129.9, 126.9, 125.5, 112.3, 111.2, 44.1, 43.3; IR (KBr, cm^{-1}) ν 2921, 2850, 1667, 1586, 1510, 1394, 1344, 1261, 1189, 1113, 1070, 948, 783; HRMS (ESI-ion trap) calcd for $C_{32}H_{26}N_6O_6Na$ [M + Na]$^+$, 613.1806; found, 613.1806.

8. Yellow solid; 90 mg; 20% yield; mp 265−266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.52−7.36 (m, 3H), 6.59 (m, 2H), 6.51 (d, J = 7.7 Hz, 1H), 6.32−6.20 (m, 3H), 6.14 (d, J = 7.9 Hz, 1H), 3.29 (s, 4H), 3.24 (s, 4H), 3.22 (s, 4H), 3.17 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 164.7, 162.3, 159.9,

DOI: 10.1021/acs.joc.5b01722
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159.4, 158.9, 158.5, 158.2, 139.4, 139.3, 139.2, 136.3, 122.3, 118.4, 118.0, 117.0, 102.5, 102.1, 100.5, 99.8, 37.3, 36. 9, 36.6, 36.6; IR (KBr, cm^{-1}) ν 2864, 1663, 1598, 1568, 1477, 1423, 1374, 1263, 1132, 1079, 980, 794, 735, 615, 545; HRMS (ACPI-ion trap) calcd for $C_{25}H_{25}N_8O$ $[M + H]^+$, 453.2146; found, 453.2142; Elemental Anal. Calcd (%) for $C_{25}H_{24}N_8O$ C 66.36, H 5.35, N 24.76; Found C 66.37, H 5.38, N 24.62.

9. Yellow solid; 120 mg; 25% yield; mp 202−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 8.2 Hz, 2H), 6.38 (d, J = 8.0 Hz, 2H), 6.28 (d, J = 7.9 Hz, 2H), 3.28 (s, 6H), 3.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 163.5, 161.9, 159.1, 158.6, 139.8, 139.4, 138.2, 122.0, 116.1, 105.8, 102.4, 38.1, 36.7; IR (KBr, cm^{-1}) ν 2858, 1683, 1580, 1474, 1451, 1415, 1383, 1342, 1117, 1070, 954, 821, 775, 740, 692, 563; HRMS (ACPI-ion trap) calcd for $C_{26}H_{25}N_8O_2$ $[M + H]^+$, 481.2095; found, 481.2093; Elemental Anal. Calcd (%) for $C_{26}H_{24}N_8O_2$ C 64.99, H 5.03, N 23.32; Found C 64.78, H 5.04, N 23.31.

10. White solid; 67 mg; 14% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 6.54 (d, J = 8.2 Hz, 2H), 6.32 (d, J = 8.1 Hz, 2H), 6.22 (d, J = 8.0 Hz, 2H), 3.30 (s, 6H), 3.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 164.3, 162.0, 159.7, 158.2, 139.9, 137.1, 123.8, 120.1, 101.4, 100.4, 37.0, 36.6; IR (KBr, cm^{-1}) ν 2922, 2851, 1677, 1601, 1561, 1478, 1425, 1381, 1261, 1132, 1081, 809, 741; HRMS (ACPI-ion trap) calcd for $C_{26}H_{25}N_8O_2$ $[M + H]^+$, 481.2095; found, 481.2093; Elemental Anal. Calcd (%) for $C_{26}H_{24}N_8O_2$ C 64.99, H 5.03, N 23.32; Found C 65.05, H 5.21, N 22.90.

11. Yellow solid; 54 mg; 10% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 10.02 (s, 4H), 7.95 (d, J = 8.2 Hz, 4H), 6.42 (d, J = 8.3 Hz, 4H), 3.50 (s, 6H), 3.31 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 120 °C) δ 187.5, 160.5, 159.5, 140.9, 117.3, 110.1, 35.1; IR (KBr, cm^{-1}) ν 2860, 1695, 1669, 1600, 1559, 1455, 1367, 1302, 1244, 1147, 1082, 967, 810, 717; HRMS (APCI-ion trap) calcd for $C_{28}H_{25}N_8O_4$ $[M + H]^+$, 537.1993; found, 537.1989; Elemental Anal. Calcd (%) for $C_{28}H_{24}N_8O_4$ C 62.68, H 4.51, N 20.88; Found C 62.42, H 4.53, N 20.68.

General Procedure for the McMurry Reductive Coupling Reaction of 5 and 9. A dry 100 mL flask was charged with Zn−Cu dust (520 mg, 8 mmol for **5**; 260 mg, 4 mmol for **9**), $TiC1_4$ (0.44 mL, 4 mmol for **5**; 0.22 mL, 2 mmol for **9**) and THF (10 mL). Under argon protection, the mixture was refluxed for 2 h to form a black slurry. Then, a solution of **5** or **9** (0.1 mmol) in the THF (20 mL) was added in one portion to the reaction mixture. The resulting mixture was refluxed for another 3.5 h; then, it was cooled to room temperature, quenched with saturated sodium carbonate (30 mL), and filtrated over a pad of florisil. The solvent was evaporated, and the residue was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried and evaporated. The residue was purified by chromatography on a silica gel column using a mixture of dichloromethane and acetone (4:1 for **14**, 10:1 for **15**) as eluent to give **14** and **15**. High quality single crystals of **14** and **15** were obtained by diffusing hexane into the solutions of **14** and **15** in chloroform.

14. White solid; 33 mg; 65% yield; mp 291−292 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 2H), 7.17 (t, J = 8.0 Hz, 2H), 6.69 (dd, J = 7.6, 1.5 Hz, 2H), 6.24 (s, 4H), 4.78 (s, 2H), 3.32 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152. 5, 149.5, 132.6, 129.8, 119.8, 115.2, 114.0, 37.7; IR (KBr, cm^{-1}) ν 2893, 1600, 1563, 1490, 1465, 1419, 1380, 1318, 1236, 1191, 1111, 1014, 773, 727, 696, 486; HRMS (APCI-ion trap) calcd for $C_{30}H_{27}N_6$ $[M + H]^+$, 471.2292; found, 471.2288; Elemental Anal. Calcd (%) for $C_{30}H_{26}N_6$ C 76.57, H 5.57, N 17.86; Found C 76.58, H 5.70, N 17.65.

15. White solid; 19 mg; 42% yield; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.35 (m, 4H), 6.64 (s, 2H), 6.55 (d, J = 7.6 Hz, 2H), 6.15 (d, J = 8.1 Hz, 1H), 6.13 (d, J = 8.0 Hz, 1H), 3.26 (s, 6H), 3.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 158.2, 156.9, 156.4, 142.4, 139.2, 134.0, 133.6, 126.6, 116.4, 98.6, 96.6, 37.1, 34.9; IR (KBr, cm^{-1}) ν 3395, 2948, 1573, 1466, 1391, 1328, 1266, 1118, 1029, 957, 772; HRMS (ESI-ion trap) calcd for $C_{26}H_{25}N_8$ $[M + H]^+$, 449.2199; found, 449.2199.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01722.

CIF file for **15** (CIF)
CIF file for **14** (CIF)
CIF file for **3** (CIF)
CIF file for **11** (CIF)
CIF file for **5** (CIF)
^{1}H and ^{13}C NMR spectra of all products, and X-ray structures of **3**, **5**, **11**, **14** and **15** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (20111310651, 20141311257, 20141321039), Ministry of Science and Technology (20111970268), and Tsinghua University for financial Support.

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DOI: 10.1021/acs.joc.5b01722
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