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Synthesis, Structure, and Conformation of Aza[1$_n$]metacyclophanes

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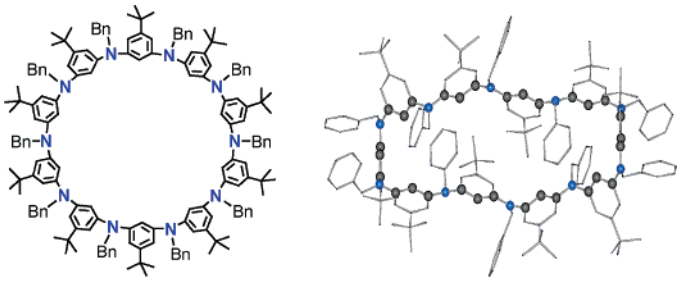
Received October 3, 2007



N-Benzyl substituted aza[1$_n$]metacyclophanes (n = 4, 6, 8, and 10) were prepared in overall 40% isolated yields via Pd-catalyzed aminations. Analyses of the reaction mixtures showed that aza[1$_4$]metacyclophane and the related polymer were the primary products (~60% overall yield); aza[1$_n$]metacyclophanes up to n = 14 and linear oligomers with up to 20 nitrogen atoms (with at least three types of end groups) were detected. Macrocyclic structures for n = 4, 6, and 10 were confirmed by X-ray crystallography. 1,3-Alternate (D_{2d}) and 1,3,5-alternate (S_6) conformations in solution on NMR time scale at low temperatures were found for macrocycles with n = 4 and n = 6, respectively; the barrier for ring inversion was considerably lower for the larger macrocycle.

Introduction

[1$_n$]Metacyclophanes (calix[*n*]arenes) and their derivatives have been widely used for the complexation of molecules and ions, gas inclusion in the solid state, scaffolds for control of dipolar interactions, as well as scaffolds for multivalent ligands and other biomedical and materials applications.[1−4] The heteroatom-bridged [1$_n$]metacyclophanes, in which the methylene bridges are replaced by heteroatoms such as sulfur, silicon, oxygen, phosphorus, and nitrogen, have recently attracted much interest. Such heteroatom-bridged macrocycles provide an opportunity to fine-tune the binding properties as a result of the distinct conformations, due to ring sizes and bond angles of the bridging atoms, as well as the binding properties of the heteroatoms. However, because of difficult synthesis, only a few heteroatom-bridged calix[*n*]arenes are known.[5,6]

With our recent success in the design and synthesis of [1$_4$]-metacyclophane-based very high-spin molecules and polymers,[7−10] including the polyarylmethyl polymer with magnetic ordering,[11] we considered aza[1$_n$]metacyclophanes (azacalix[*n*]arenes) as building blocks for robust high-spin polyradicals, in which the highly reactive carbon-centered radicals are replaced with nitrogen-centered radicals.

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10.1021/jo702151n CCC: $40.75
Published on Web 12/06/2007

Aza[1_n]metacyclophanes may be viewed as macrocyclic oligomers of poly(*m*-aniline).[12−16] Linear and star-branched oligomers of secondary diarylamines, in which NH groups are connected via *m*-phenylene units, have been studied as precursors for aminyl ($R_2N^{\bullet}$),[17] aminium ($R_3N^{\bullet+}$),[18,19] and nitroxide ($R_2NO^{\bullet}$) polyradicals.[20]

The recent development of Pd-catalyzed aminations[21,22] provides efficient synthetic routes to N-substituted aza[1_n]-metacyclophanes (N(R)-bridged aza[1_n]metacyclophanes).[23−30] However, very few aza[1_n]metacyclophanes that are macrocyclic oligomers of secondary diarylamines (N(H)-bridged aza[1_n]-metacyclophanes) have been reported.[23] Although aza[1_4]-metacyclophane (Figure 1) was first reported by Smith in 1963,[31] recent attempts at the preparation of aza[1_4]metacyclophane by Pd-catalyzed aminations resulted only in trace amounts of the macrocycle in the reaction mixtures, and no N(H)-bridged aza-[1_4]metacyclophane was isolated, even if dilute conditions were used.[23]

Herein, we report the efficient synthesis of N(H)-bridged aza-[1_4]metacyclophanes (Figure 2). Our synthetic route involves *N*-benzyl protection of the secondary diarylamines and their effective removal following Pd-catalyzed amination. We include 5-*t*-butyl substituents to provide enhanced solubility, thus facilitating the preparation of higher aza[1_n]metacyclophanes as well as a detailed analysis of poly(*m*-aniline). This synthetic approach provided aza[1_n]metacyclophanes with $n = 4$, 6, 8, and 10. Aza[1_n]metacyclophanes ($n = 4$, 6, and 10) were characterized by X-ray crystallography. Conformation and dynamics for aza[1_n]metacyclophanes ($n = 4$ and 6) were studied by variable temperature NMR spectroscopy.

To our knowledge, aza[1_n]metacyclophanes with $n > 8$, as well as conformations and dynamics of any aza[1_n]-metacyclophanes in solution, have not been reported. *N*-Benzyl substituents in aza[1_n]metacyclophanes in Figure 2 provide a probe for the symmetry point groups of their conformations and for the barriers of macrocyclic ring inversions by distinguishing between diastereotopic and enantiotopic methylene protons with variable temperature ^{1}H NMR spectroscopy.

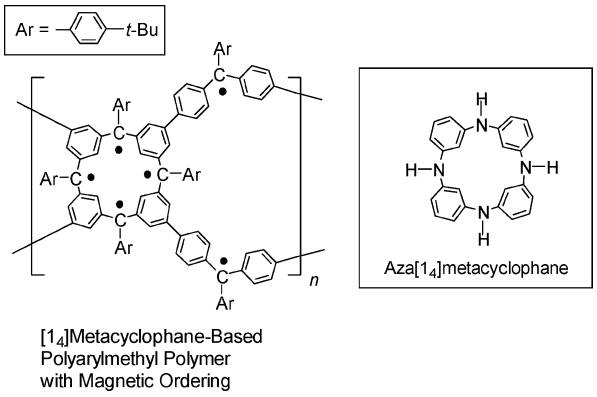

FIGURE 1. [1_4]Metacyclophanes.

Results and Discussion

Synthesis. Two synthetic routes to aza[1_n]metacyclophanes were explored (Scheme 1). Both routes relied on the condensation of diaminobenzenes and dibromobenzenes via a C−N bond coupling reaction, using conditions that are similar to those for triarylamine-based azacyclophanes with alternating *m*- and *p*-phenylenes.[32,33] Low concentrations of monomers were used to optimize the formation of macrocyclic products. The final step to form aza[1_n]metacyclophane in route A requires *n* CN bond couplings, as compared to *n*/2 CN bond couplings in route B. However, route A provides significantly higher yields of aza-[1_n]metacyclophanes. Condensations of 1,3-dibromobenzene **3** with benzyl-protected 1,3-diaminobenzene **4** at 1 mM concentrations gave more than 40% isolated yields of aza[1_n]-metacyclophanes ($n = 4$, 6, 8, and 10), in addition to the corresponding polymer **2**.[34] The analyses of the crude reaction mixtures indicate that the relative content of the major aza[1_n]-metacyclophanes ($n = 4$, 6, and 8) is 10:3:1 (Table S5, Supporting Information), which approximately corresponds to their isolated yields.

In route B, condensations of benzyl-protected 1,3-diaminobenzene **4** at ∼10 mM concentrations with bis(bromobenzene) **5** resulted in lower yields of aza[1_n]metacyclophanes with the relative content of 10:1 for the major aza[1_n]metacyclophanes ($n = 4$ and 8).

Isolation of the aza[1_n]metacyclophanes starts with filtration of the crude reaction mixture through silica, followed by debenzylation with Pd/C and ammonium formate, and then separation by column chromatography on deactivated silica, to provide **1-[N4]H**, **1-[N6]H**, and **1-[N8]H** in 31, 9, and ∼3% isolated yields, respectively. Because the *N*-benzyl substituted diarylamines undergo deprotection readily on silica, the isolated

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(34) Aza[1_{12}]metacyclophane was isolated as well, but it was not fully characterized.

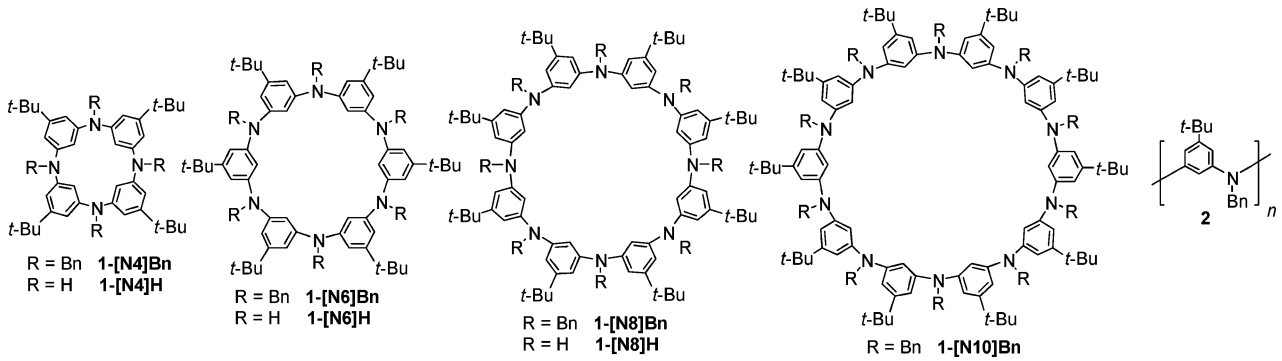
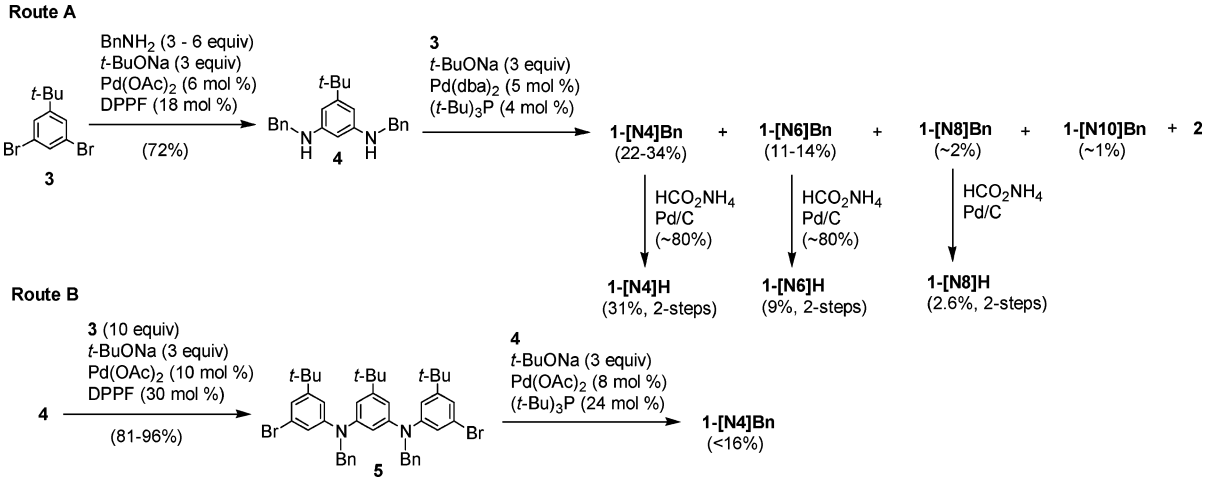


FIGURE 2. Aza[1$_n$]metacyclophanes and corresponding polymer.

SCHEME 1. Synthesis of Aza[1$_n$]metacyclophanes



yields (and purities) of the desired products are dependent on the purification procedure (Supporting Information).

Both macrocyclic products and crude reaction mixtures for condensations by route A were characterized by gel permeation chromatography with multiangle light scattering, mass spectrometry, NMR spectroscopy, and X-ray crystallography.

Gel Permeation Chromatography with Multiangle Light Scattering (GPC/MALS). GPC/MALS provides an absolute measure of weight average molecular weight (M_w) mass and a column-dependent measure of number average molecular weight (M_n).[35] The crude reaction mixtures, obtained by route A, have $M_w \approx 5$ kDa and polydispersity indices PDI ≈ 1.7 (PDI $= M_w/M_n$). A typical chromatogram consists of a tall peak at the elution time corresponding to aza[1$_4$]cyclophane **1-[N4]Bn**, with a shoulder coinciding with **1-[N6]Bn**, and a broad, intense peak at longer elution times. The last peak corresponds to polymer **2** and related oligomers, with a broad distribution of molecular weights (Figure 3).

The elution time of **1-[N4]Bn** is longer than that of **1-[N6]Bn**, reflecting the smaller hydrodynamic radius for **1-[N4]Bn**, as compared to **1-[N6]Bn**. For both cyclophanes, the measured values of M_w are within 5% of the formula masses, which is an excellent agreement;[36] also, the PDI is close to 1.00, as expected for monodisperse oligomers (Table S2, Supporting Information). These results indicate that macrocycles **1-[N4]Bn** and **1-[N6]Bn** and polymer **2** are the major products for condensations by route A.

Mass Spectrometry. The crude reaction mixtures were analyzed by both FAB MS and ESI MS. For the reaction mixtures obtained by route A, the molecular ions corresponding to the macrocycles with $n = 4$ and $n = 6$ were dominant in the mass spectra (Figures S2A−C and S3A, Supporting Information). Within uncertainties of the relative ionization efficiencies in MS, this result is consistent with GPC/MALS data. The higher resolution of the MS provides insight into the structure of polymer **2**, which is composed of both higher macrocycles and linear oligomers.

In FAB MS, monocharged isotopic clusters for M^+ ions of macrocycles up to $n = 12$ were well-resolved; the M^+ ion for $n = 14$ was detected, but the isotopic pattern was not well-resolved (Table S3 and Figure S2A−C, Supporting Information). In addition to the macrocycles, relatively less intense molecular ions for three series of linear oligomers, labeled as A−C (Figure 4), were detected with well-resolved isotopic patterns up to $n = 8-10$.

In ESI MS, multiply charged isotopic clusters for molecular ions of the macrocycles and of the linear oligomers A−C were detected (Table S4 and Figure S3A, Supporting Information). The presence of macrocycles with up to $n = 14$ was established by the M^{3+} cluster for $n = 14$ with a well-resolved isotopic pattern; partially resolved M^{2+} and M^{4+} clusters support this

(35) Absolute molecular weight of polyaniline by light scattering: Kolla, H. S.; Surwade, S. P.; Zhang, X.; MacDiarmid, A. G.; Manohar, S. K. *J. Am. Chem. Soc.* **2005**, *127*, 16770−16771.

(36) Agreement between experimental and nominal molecular weights indicates that the elution from the GPC columns is practically complete for **1-[N4]Bn** and **1-[N6]Bn**.

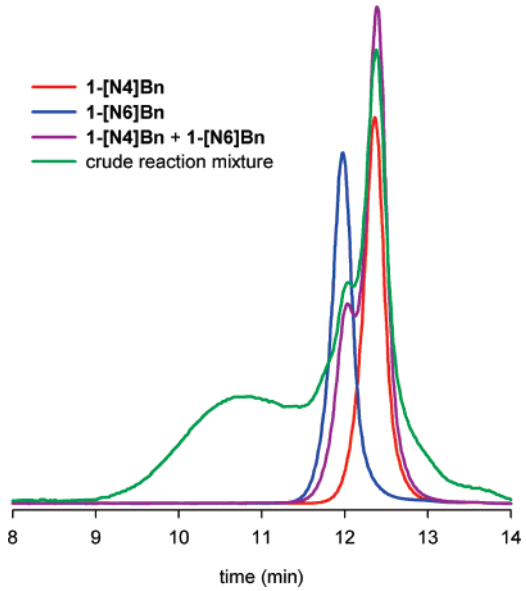
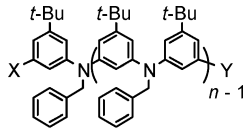


FIGURE 3. Gel permeation chromatography of aza[1_4]cyclophane **1-[N4]Bn**, aza[1_6]cyclophane **1-[N6]Bn**, mixture of **1-[N4]Bn** and **1-[N6]Bn**, and crude reaction mixture. Only plots from the refractive index detector are shown.



Series **A**, X = *t*-BuO, Y = H
Series **B**, X = Y = *t*-BuO
Series **C**, X = Y = H

FIGURE 4. Linear oligomers detected by FAB MS and ESI MS in the crude reaction mixtures (route A).

assignment (Figure S3B−D, Supporting Information). The assignments of the higher macrocycles with $n = 16$ (M^{3+} and M^{5+} clusters) and $n = 18$ (M^{4+} cluster), based on partially resolved isotopic patterns, are tentative. In the high mass range, the isotopic clusters corresponding to the molecular ions for linear oligomers A are relatively more intense than those corresponding to the macrocycles; oligomers A with up to 20 nitrogen atoms are detectable.

^{1}H NMR Spectroscopy. The aromatic regions of ^{1}H NMR spectra of crude reaction mixtures (route A) show well-resolved doublets and triplets (1:2, $J \approx 2$ Hz) for aza[1_n]metacyclophanes ($n = 4$, 6, and 8), with $n = 4$ as the dominant product (Figure 5 and Table S5, Supporting Information). The resonances for higher macrocycles, $n = 10$ and 12, and the polymer coincide within intense, broadened doublet- and triplet-like multiplets at δ 6.62 and 6.48 ppm. Other relatively low-intensity resonances were analyzed with the aid of a COSY spectrum; in the 6.2−7.2 ppm region, at least five three-proton spin systems and two four-proton spin systems may be assigned to distinct linear oligomers and their end groups (Figure S4A−C and Table S6, Supporting Information). These assignments are consistent with the presence of macrocycles and linear oligomers, series A−C, detected by MS.

Crystal Structures. Structures for aza[1_n]metacyclophanes ($n = 4$, 6, and 10) were determined using X-ray crystallography (Table S1 and Figures 6 and 7).

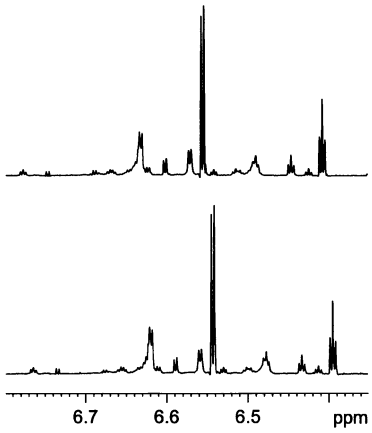


FIGURE 5. ^{1}H NMR (600 MHz, chloroform-*d*) spectra for two representative crude mixtures from the condensation reaction (route A). The sample concentrations are ∼20 and ∼3 mg/mL in the top (LB = −1.00 Hz and GB = +0.60 Hz) and bottom (LB = −0.80 Hz and GB = +0.60 Hz) spectra, respectively.

Crystal structures were obtained for **1-[N4]Bn** and two solvent polymorphs of **1-[N4]H**.[37] In each structure, the macrocyclic ring adopts a calix[4]arene-like 1,3-alternate conformation with an approximate S_4 point group;[38] in **1-[N4]H**, the 1,3-alternate conformations are relatively flattened (Figure 6).[39−41] The 1,3-alternate conformation is similar to that reported for the N-methylated derivative of aza[1_4]metacyclophane in the solid state.[42] These conformations are different from the chair-like conformations reported for [1_4]metacyclophane macrocycles in the solid state.[43,44]

In crystal structures of **1-[N6]Bn** and **1-[N10]Bn**, the asymmetric unit contains half of the molecule, and no solvent is included, even though for **1-[N10]Bn**, a void of approximately 50 Å^3 with no significant electron density is present. Both molecules have an exact (crystallographic) inversion center (*i*). The $n = 6$ macrocycle adopts a 1,3,5-alternate conformation with an approximate S_6 point group of symmetry.[38] For the $n = 10$ macrocycle, the torsion angles along the macrocyclic ring are similar to those for the $n = 6$ macrocycle, except for the linker arylamine units as indicated with arrows in Figure 8.

(37) One of the solvent polymorph structures for **1-[N4]H**, with two molecules per asymmetric unit, is of lower quality, and it should be viewed as a supporting structure. A brief description of this structure is provided in the Supporting Information.

(38) Torsion angles for bis(benzylamino)benzene moieties (Figure 11), with approximate Sn point groups of symmetry for the aza[1_n]metacyclophane macrocycles: **1-[N4]Bn**, C6−C1−N1−C41 = 154.76(15)°, C6−C5−N2−C48 = −98.31(18)°, C16−C11−N2−C48 = −177.84(14)°, C16−C15−N3−C55 = 130.17(16)°, C26−C21−N3−C55 = 160(4)°, C26−C25−N4−C62 = −102(4)°, C36−C31−N4−C62 = −179.28(14)°, C36−C35−N1−C41 = 127.65(16)°; **1-[N6]Bn**, C13−C8−N1−C1 = −163.42(14)°, C13−C12−N2−C18 = −72.11(19)°, C30−C25−N2−C18 = 171.88(14)°, C30−C29−N3−C35 = 19.9(2)°, C47−C42−N3−C35 = −140.09(16)°, C1−N1−C46$^{\#1}$−C47$^{\#1}$ (with symmetry operation #1: $-x, -y, 1 - z$) = −65.5(2)°.

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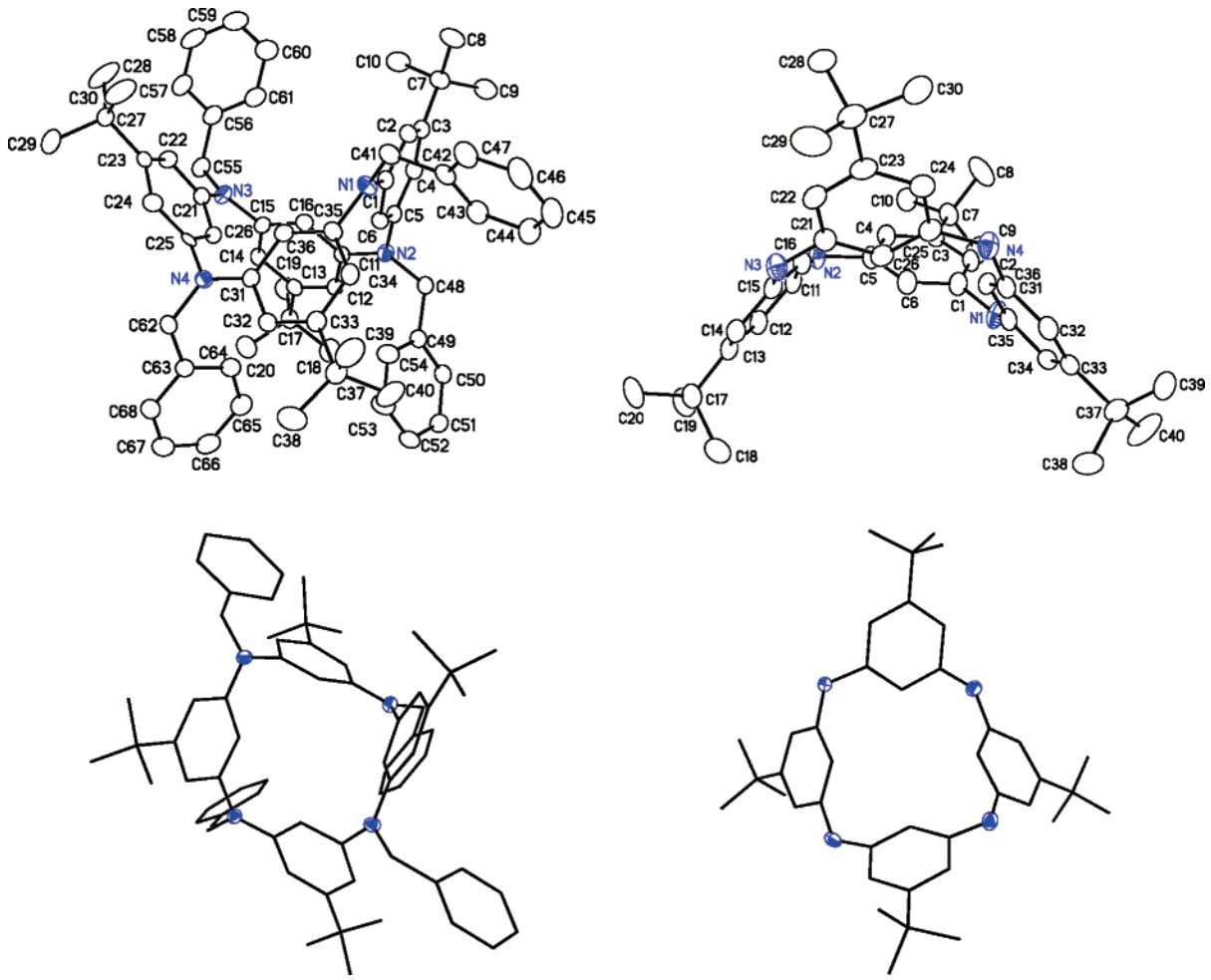

FIGURE 6. Molecular structure aza[1$_n$]metacyclophanes (n = 4) **1-[N4]Bn** and **1-[N4]H**. Carbon and nitrogen atoms are depicted with thermal ellipsoids (50% probability level). Hydrogen atoms, disorder and in **1-[N4]H** incorporated solvent are omitted for clarity.

The 1,3,5-alternate conformation in **1-[N6]Bn** is similar to that found in calix[6]pyrrole derivatives.[45] The conformations found for **1-[N6]Bn** and **1-[N10]Bn** are different from typical conformations reported for calix[6]arenes and calix[10]arenes in the solid state.[46,47]

Variable Temperature ^{1}H NMR Spectroscopy. ^{1}H NMR spectra of **1-[N4]Bn** in chloroform-*d* at 298 K indicate the tetra-fold symmetric molecular conformation, including the 2-fold symmetry for all benzene rings. Notably, the resonance for the benzylic methylene protons appears as a broad singlet. At lower temperatures, the benzylic methylene protons become diastereotopic, showing an AB-spin system with a geminal coupling constant, $|J|$ = 17 Hz, and frequency difference, $\Delta\nu$ = 140 Hz at 500 MHz (Figure 9). All other ^{1}H resonances are unchanged, and they too are compatible with the tetra-fold symmetric conformation, including the two-fold symmetry for all benzene rings, on the NMR time scale in the 215−330 K range. Similarly, the ^{13}C NMR spectra at 298 and 215 K with eight resonances in the aromatic region support the proposed molecular symmetry (Figure S7A,B, Supporting Information). On the basis of the coalescence temperature, T_{coal} = 301 K, of the benzylic methylene protons, a free energy barrier of 14.2 ± 0.1 kcal mol^{-1} for ring inversion was estimated.[48] This is in good agreement with the enthalpy of activation ΔH_{act} = 14.1 ± 0.8 kcal mol^{-1} and the negligible entropy of activation (ΔS_{act} = −0.1 ± 2.7 cal mol^{-1} K^{-1}), which were obtained by the line shape analysis of 10 ^{1}H NMR spectra in the 265−330 K range (Figure S5, Supporting Information).[49] The conformational mobility of **1-[N4]Bn** is considerably lower than that of the

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(46) Conformations for derivatives of calix[6]arenes in the solid state were described as winged cone, pinched cone, double partial cone, distorted 1,2,3-alternate, and 1,2,4,5-alternate: (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; Ch. 4, pp 60−61. (b) Janssen, R. G.; van Duynhoven, J. P. M.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, *118*, 3666−3675.

(47) Conformations for derivatives of calix[10]arenes in the solid state were described as pinched cone and pleated loop: Perrin, M.; Ehlinger, N.; Viola-Motta, L.; Lecocq, S.; Dumazet, I.; Bouoit-Montesino, S.; Lamartine, R. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *39*, 273−276.

(48) (a) Rate constants at the coalescence temperatures (k_{coal}) are obtained from the approximate equation for AB-systems, $k_{coal} = (\pi/2^{1/2})[(\Delta\nu^2 + 6J^2)^{1/2}]$. For other ^{1}H spin systems, in which $|J|$ is negligible as compared to $\Delta\nu$, and for ^{13}C NMR coalescences, the value coupling constant is set to zero (i.e., $k_{coal} = (\pi/2^{1/2})\Delta\nu$). Free energy barriers are estimated using the Eyring equation, with the transmission coefficient set to one. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Ch. 8, pp 502−507.

(49) DNMR simulations were performed with a version of the computer program WINDNMR (Reich, H. J. *J. Chem. Educ. Software* **1996**, *3*, 2; http://www.chem.wisc.edu/areas/reich/plt/windnmr.htm).

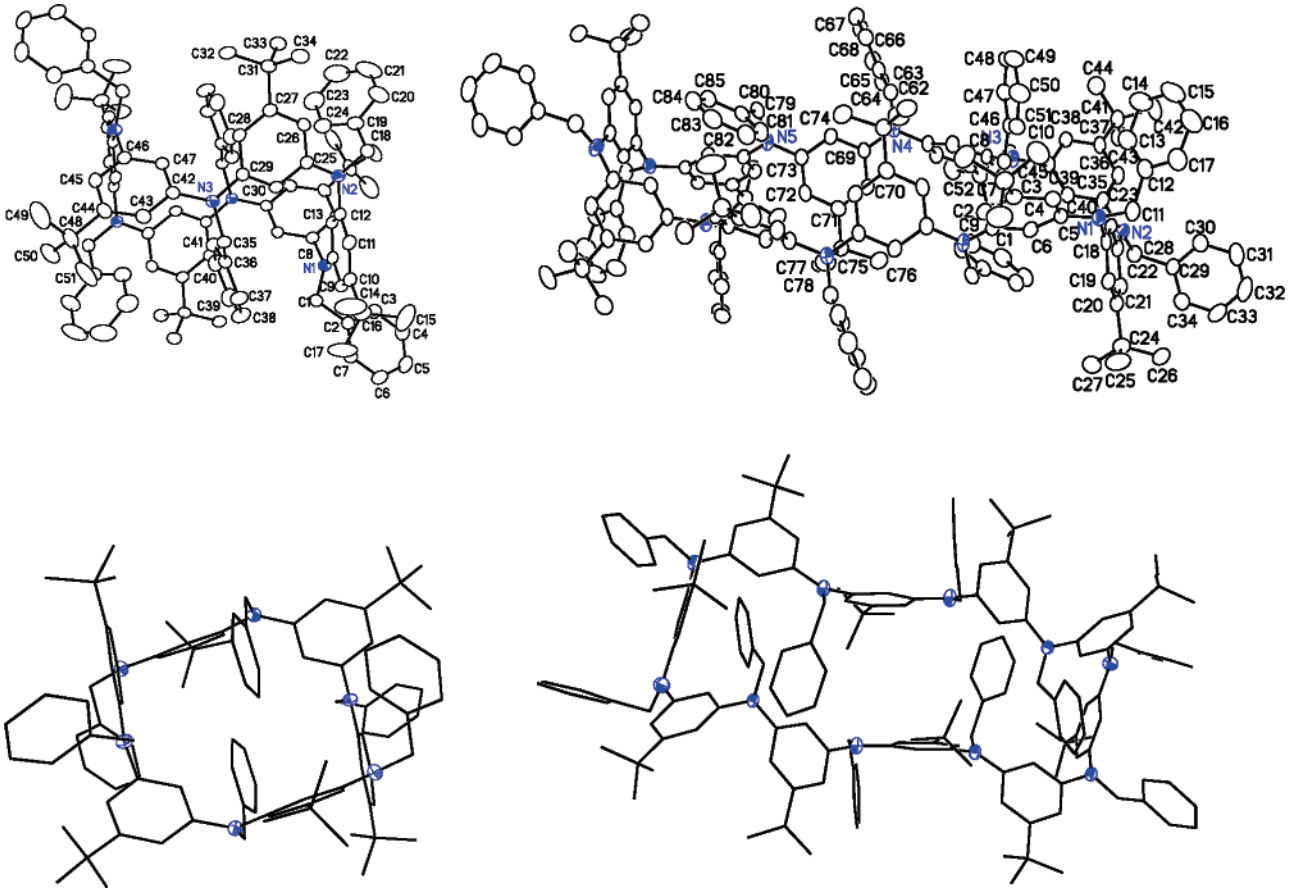

FIGURE 7. Molecular structure of aza[1_n]metacyclophanes (n = 6 and 10) **1-[N6]Bn** and **1-[N10]Bn**. Carbon and nitrogen atoms are depicted with thermal ellipsoids set at the 50% probability level. Hydrogen atoms are omitted for clarity.

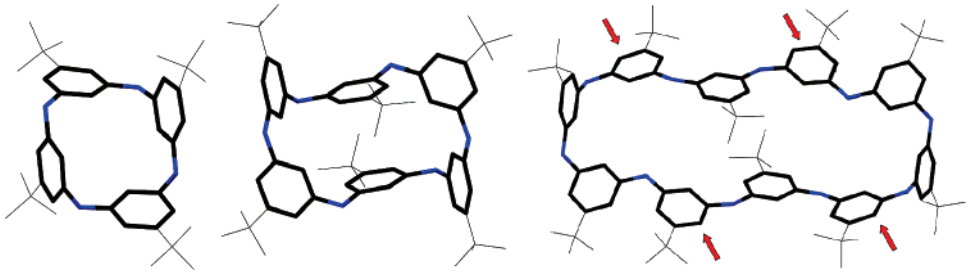

FIGURE 8. Conformations of macrocyclic rings of aza[1_n]metacyclophanes (n = 4, 6, and 10) in crystalline **1-[N4]Bn**, **1-[N6]Bn**, and **1-[N10]Bn**. Benzyl groups and hydrogens are omitted for clarity. For n = 10, arrows indicate linker arylamine units.

analogous calix[4]arene devoid of hydroxyl groups, for which the free energy barrier is less than 9.5 kcal mol^{-1}.[43,50]

The NMR spectra of **1-[N4]Bn** in chloroform-*d* at low temperature support the assignment of a 1,3-alternate conformation with a D_{2d} point group on the NMR time scale.[51] The D_{2d} point group has two additional symmetry elements (two symmetry planes σ_d), as compared to the approximate S_4 point group found in the solid state. The σ_d planes render the benzene rings two-fold symmetric. The benzylic methylene protons are not related by any element of symmetry, and therefore, they are diastereotopic in the D_{2d} symmetric conformation. At higher temperatures, the average structure on the NMR time scale for **1-[N4]Bn** has to possess two additional symmetry planes σ_v dissecting the diagonal N-Bn moieties. In such an averaged structure (e.g., a cone with a C_{4v} point group), the benzylic methylene protons are enantiotopic, thus appearing as a singlet in the ^{1}H NMR spectra at higher temperatures.

The ^{1}H NMR spectrum of **1-[N6]Bn** in chloroform-*d* at 298 K indicates a hexa-fold symmetric conformation, with two-fold symmetry for all benzene rings; all resonances including the singlet for the benzylic methylene protons are sharp. At lower temperatures, the singlet for the benzylic methylene protons at 4.76 ppm becomes an AB-system ($|J|$ = 17 Hz, $\Delta\nu$ = 71 Hz at 500 MHz, 243 K), and the aromatic doublet ($|J|$ = 2 Hz) at 6.559 ppm splits into two singlet-like resonances ($\Delta\nu$ = 150 Hz at 500 MHz, 228 K); the coalescence temperatures were

(50) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; Ch. 4, p 65.

(51) Structure of **1-[N4]Bn** with the D_{2d} point group is either a minimum on the potential energy surface or an averaged structure on the NMR time scale, resulting from the fast exchange between structures with S_4 point groups.

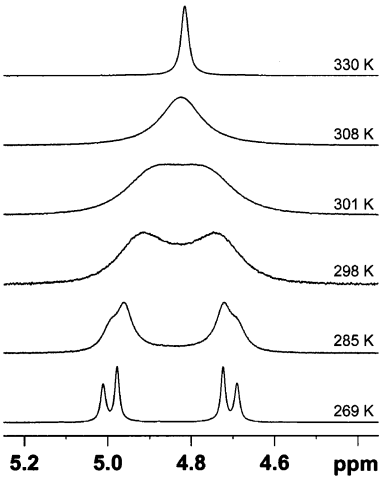

FIGURE 9. Partial ^{1}H NMR (500 MHz, chloroform-*d*, 269−330 K) spectra of the benzylic methylene region in **1-[N4]Bn**.

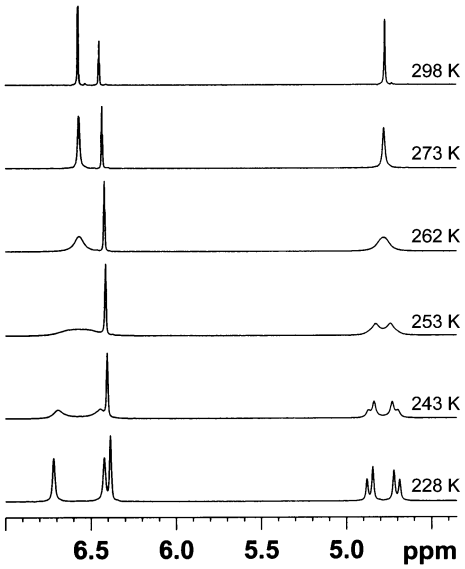

FIGURE 10. Partial ^{1}H NMR (500 MHz, chloroform-*d*, 228−298 K) spectra of the benzylic methylene and aromatic regions in **1-[N6]Bn**.

found at approximately 258 and 250 K, respectively (Figure 10). The line shape analyses of the resonances for the benzylic methylene protons in seven ^{1}H NMR spectra in the 243−298 K range provide $\Delta H_{act} = 11.3 \pm 0.9$ kcal mol^{-1} and $\Delta S_{act} \approx -4.4 \pm 3.6$ cal mol^{-1} K^{-1} (Figure S6, Supporting Information),[49] which are in good agreement with $\Delta G_{act} \approx 12.4 \pm 0.1$ kcal mol^{-1} at $T_{coal} = 258$ K.[48] Siginificantly lower $\Delta G_{act} \approx 11.7 \pm 0.1$ kcal mol^{-1} at $T_{coal} = 250$ K was obtained for the conformational process involving aromatic protons.

The ^{13}C NMR spectrum for **1-[N6]Bn** at 298 K indicates hexa-fold symmetry with two-fold symmetry for the benzene rings; however, two of the eight resonances in the aromatic region at 149.4 and ~111 ppm were broadened; at 215 K, two pairs of new resonances at 149.9 and 147.0 ppm ($\Delta\nu = 365$ Hz) and at 113.6 and 107.0 ppm ($\Delta\nu = 830$ Hz) were obtained. For the first pair of resonances, $T_{coal} = 260$ K was reasonably well-determined, giving $\Delta G_{act} \approx 11.7$ kcal mol^{-1}, which is in excellent agreement with the barrier obtained from ^{1}H NMR spectra. For the second pair of resonances, $T_{coal} = 270$ K, which is within the expected range, gave a similar value of ΔG_{act} (Figures S9A−F and S10, Supporting Information). Two-

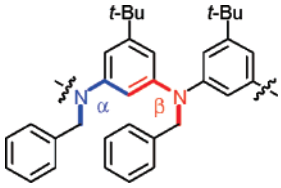

FIGURE 11. Torsion angles α and β.

dimensional ^{1}H−^{1}H COSY and ^{1}H−^{13}C HMQC spectra at 238 K confirm that the aromatic protons and carbons, which possess coalescing resonances at higher temperatures, are associated with a single spin system (Figure S8A,B, Supporting Information).

These results indicate that **1-[N6]Bn** in chloroform-*d* at low temperatures adopts a 1,3,5-alternate conformation with an S_6 point group of symmetry. Thus, conformations for the $n = 6$ macrocycle in solution and in the solid state are similar (Figure 8). At higher temperatures, two distinct conformational processes with $\Delta G_{act} \approx 11.7 \pm 0.1$ kcal mol^{-1} and $\Delta G_{act} \approx 12.4 \pm 0.1$ kcal mol^{-1} led to averaged structures with a higher symmetry on the NMR time scale.

The process with lower ΔG_{act}, which exchanges selected nuclei in the *t*-butylbenzene rings, led to the averaged structure with three σ_d planes, thus rendering the benzene rings two-fold symmetric. This process of exchanging the S_6 symmetric conformations to provide an average structure with a D_{3d} point group may be described as the conformational motion averaging of two torsion angles (α and β) associated with each bis-(benzylamino)benzene moiety of the macrocycle (Figure 11). In the 1,3,5-alternate conformation with the S_6 point group, α and β may have different values within each moiety ($\alpha \neq \beta$), with alternating signs between the adjacent moieties. In the D_{3d} point group, α and β must have identical values within each moiety ($\alpha = \beta$), with alternating signs between the adjacent moieties, thus leading to two-fold symmetric benzene rings.

The process with higher ΔG_{act}, exchanging the benzylic methylene protons, leads to an averaged structure with three σ_v planes dissecting diagonal N-Bn moieties, thus rendering the benzylic methylene protons enantiotopic. This process of macrocyclic ring inversion provides an average structure on the NMR time scale, which may correspond to a C_{6v} symmetric cone. The barrier for ring inversion is considerably lower for the $n = 6$ macrocycle than that for the $n = 4$ macrocycle.[52]

Similarly, there are examples of derivatives of calix[6]arenes that have similar structures in the solid state and in solution.[46,53] Also, derivatives of calix[6]arenes possess a significantly greater conformational mobility as compared to those of calix[4]-arenes.[53,54]

Experimental Section

ESI MS. Studies were carried out on a time-of-flight mass spectrometer. The solvent system used for all experiments was trifluoroacetic acid (0.1−3%) in dichloromethane (HPLC grade).

(52) ^{1}H NMR spectrum for **1-[N8]Bn** in chloroform-*d* is well-resolved, showing a singlet for the benzylic methylene protons, in the 298−260 K range. Also, the ^{13}C NMR spectrum for **1-[N8]Bn** in chloroform-*d* shows no broadening at 298 K (Figure S11, Supporting Information). This might suggest that the $n = 8$ macrocycle might even be more conformationally mobile than the $n = 6$ macrocycle.

(53) Molins, M. A.; Nieto, P. M.; Sanchez, C.; Prados, P.; de Mendoza, J.; Pons, M. *J. Org. Chem.* **1992**, *57*, 6924−6931.

(54) van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814−5822.

Concentrations of samples injected were 10^{-5} to 10^{-6} M. Flow rates (5−20 μL min^{-1}) were controlled by a syringe pump. Samples of isolated amines were prepared using an acidic solvent system. Samples of crude reaction mixtures were stirred and diluted in dichloromethane with the final dilution performed with the acidic solvent mixture.

GPC/MALS. A 17-angle light scattering detector and interferometric refractive index detector were used for GPC/MALS studies. Two 4.6 mm × 300 mm 5-μ GPC columns (500 Å and following in a sequence 10^3 Å), with THF as the mobile phase, were used. The flow rate of THF was 0.5 mL/min, and d*n*/d*c* was computed on-line. Solutions of oligomer, polymer, or a crude mixture in THF (100 μL) were injected into a 20 μL loop, typically 3 times.

X-ray Crystallography. Crystals for X-ray studies were prepared from solutions of solvent precipitant mixtures. Data collections were performed on a platform diffractometer equipped with a SMART 6000 detector using Mo Kα radiation (graphite monochromator). Final cell constants were calculated from the *xyz* centroids of strong reflections from the actual data collection after integration (SAINT);[55] intensity data were corrected for absorption (SADABS).[56] Space groups were determined based on intensity statistics and systematic absences. Structures were solved with direct methods (SIR-92) and refined with full-matrix least-squares/difference Fourier cycles (SHELXL-97).[57,58] All non-hydrogen atoms were refined with anisotropic displacement parameters unless noted otherwise in the CIF files. The hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. For **1-[N4]Bn** and **1-[N4]H**, disorder was refined for *t*-butyl groups and phenyl *t*-butyl groups.

Variable Temperature NMR Spectroscopy. ^{1}H NMR (500 MHz) spectra were obtained for ∼0.01 M solutions of **1-[N4]Bn** and **1-[N6]Bn** in chloroform-*d*. The line shape analyses were carried out for the AB-systems of the benzylic methylene resonances in a temperature range not too far from the coalescence temperature, such that the values of the frequency differences for the coalescing resonances were constant for each compound. The rate constants (k) were numerically fit to the Eyring equation, ln(k/T) versus 1000/T, to provide straight line fits with correlation coefficients R^2 = 0.992−0.994 and values of the activation parameters. The error bars for the enthalpy of activation and entropy of activation were based on standard errors for the slope and intercept, which were multiplied by a factor of 2.

General Procedure. Route A. A 0.001 M solution of diamine **4** (1 equiv) in toluene, containing 5-*t*-butyl-1,3-dibromobenzene **3** (1.1 equiv), Pd(dba)$_2$ (0.05 equiv), *t*-BuONa (3 equiv), and P(*t*-Bu)$_3$ (0.04 equiv), was stirred in a closed Schlenk vessel under nitrogen at room temperature. The reaction mixture was periodically monitored by TLC and ^{1}H NMR spectroscopy to follow the formation of products. After about 9 days at room temperature, the crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy, MS, and GPC, and the macrocyclic products were separated by column chromatography and/or preparative TLC. In an alternative procedure, the crude reaction mixture was filtered through silica, subjected to debenzylation, and then separated by chromatography.

Route B. A 0.01 M solution of diamine **4** (1 equiv) in toluene, containing bis(bromobenzene) **5** (1.1 equiv), Pd(OAc)$_2$ (0.08 equiv), *t*-BuONa (3 equiv), and P(*t*-Bu)$_3$ (0.24 equiv), was stirred in a closed Schlenk vessel under nitrogen at 100 °C. After 3 days at 100 °C, the crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy and FAB MS, and the macrocyclic products were separated by column chromatography and/or preparative TLC.

Debenzylation. Excess amounts of Pd/C (10% Pd wt on C) and freshly recrystallized ammonium formate were added in two portions to a solution of *N*-benzyl aza[1$_n$]metacyclophane in ethanol at reflux. After 4 h at reflux, filtration through Celite, preparative TLC, and recrystallization provided N(H)-bridged aza[1$_n$]-metacyclophane.

Tetraazacyclophane 1-[N4]Bn. White crystals from dichloromethane/methanol. Mp 206−207 °C; ^{1}H NMR (500 MHz, chloroform-*d*, 298 K): δ = 7.304 (d, J = 7, 8 H), 7.249 (t, J = 8, 8 H), 7.173 (t, J = 7, 4 H), 6.544 (d, J = 2, 8 H), 6.397 (t, J = 2, 4 H), 5.1−4.6 (d(br), 8 H), 1.107 (s, 36 H); ^{1}H NMR (500 MHz, chloroform-*d*, 215 K): δ = 7.414 (d, J = 8, 8 H), 7.342 (t, J = 8, 8 H), 7.281 (s, residual solvent peak, $CHCl_3$), 7.250 (t, J = 8, 4 H), 6.685 (s, 8 H), 6.519 (s, 4 H), 5.084, 4.740 (AB, J = 17, 8 H), 1.097 (s, 36 H); ^{13}C NMR (125 MHz, chloroform-*d*, 298 K): δ = 153.5, 148.9, 140.1, 128.3, 126.9, 126.5, 112.7, 111.0, 57.4, 34.8, 31.2; ^{13}C NMR (125 MHz, chloroform-*d*, 215 K): δ = 153.2, 147.9, 139.8, 128.4, 126.4, 126.1, 110.9, 109.9, 57.4, 34.6, 30.9; IR (ZnSe, cm^{-1}): 1582 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 200−1100, deviation from the formula) at 949.6098 ([M + 1]$^+$, 95.5, 0.6 ppm for $^{13}C_1{}^{12}C_{67}{}^1H_{76}{}^{14}N_4$), 948.6048 ([M]$^+$, 100, 2.3 ppm for $^{12}C_{68}{}^1H_{76}{}^{14}N_4$).

Hexaazacyclophane 1-[N6]Bn. White crystals from diethyl ether/hexane. Mp 265 °C; ^{1}H NMR (500 MHz, chloroform-*d*, 298 K): δ = 7.247 (s, residual solvent peak, $CHCl_3$), 7.22−7.08 (m, 30 H), 6.559 (d, J = 2, 12 H), 6.435 (t, J = 2, 6 H), 4.758 (s, 12 H), 1.101 (s, 54 H); ^{1}H NMR (500 MHz, chloroform-*d*, ^{1}H−^{1}H COSY cross-peak, 238 K): δ = 7.303 (d, J = 7, 12 H, 7.244), 7.273 (s, residual solvent peak of $CHCl_3$), 7.244 (t, J = 7, 12 H, 7.303, 7.182), 7.182 (t, J = 7, 6 H, 7.244), 6.733 (s, 6 H, 6.440, 6.405), 6.440 (s, 6 H, 6.733, 6.405), 6.405 (s, 6 H, 6,733, 6.440), 4.874, 4.724 (AB, J = 17, 12 H, 4.874, 4.724), 1.120 (s, 54 H); ^{1}H NMR (500 MHz, chloroform-*d*, 228 K): δ = 7.304 (d, J = 7.5, 12 H), 7.277 (s, residual solvent peak of $CHCl_3$), 7.246 (t, J = 7.5, 12 H), 7.184 (t, J = 7.5, 6 H), 6.734 (s, 6 H), 6.439 (s, 6 H), 6.404 (s, 6 H), 4.88, 4.72 (AB, J = 17, 12 H), 1.120 (s, 54 H); ^{1}H NMR (500 MHz, chloroform-*d*, 215 K): δ = 7.324 (d, J = 7.5, 12 H), 7.267 (t, J = 7.5, 12 H), 7.198 (t, J = 7.5, 6 H), 6.759 (s, 6 H), 6.434 (s, 6 H), 6.391 (s, 6 H), 4.888, 4.719 (AB, J = 17, 12 H), 1.125 (s, 54 H); ^{13}C NMR (125 MHz, chloroform-*d*, 298 K): δ = 153.2, 149.4 (br), 140.4, 128.3, 126.43, 126.40, ∼111 (v. br), 110.7, 57.1, 34.8, 31.2; ^{13}C NMR (125 MHz, chloroform-*d*, ^{1}H−^{13}C HMQC cross-peak, 238 K): δ = 152.4 (q), 149.9 (br, q), 147.1 (br, q), 139.7 (q), 128.3 (7.246), 126.3 (7.182), 126.0 (7.703), 113.5 (br, 6.733), 109.9 (6.405), 107.3 (br, 6.440), 56.8 (4.874, 4.724), 34.7 (q), 31.0 (1.120); ^{13}C NMR (125 MHz, chloroform-*d*, 215 K): δ = 152.3, 149.9, 147.0, 149.6, 128.3, 126.3, 125.9, 113.6, 109.7, 107.0, 56.7, 34.6, 31.0; IR (ZnSe, cm^{-1}): 1578 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 200−2050, deviation from the formula) at 1423.9160 ([M + 1]$^+$, 100, −1.5 ppm for $^{13}C_1{}^{12}C_{101}{}^1H_{114}{}^{14}N_6$), 1422.9105 ([M]$^+$, 97, 0.0 ppm for $^{12}C_{102}{}^1H_{114}{}^{14}N_6$).

Octaazacyclophane 1-[N8]Bn. White solid from benzene/methanol. Complicated melting behavior was found: 90−95 °C (white solid forms a colorless treacle), 113−115 °C (glass-like softening), and 221−228 °C (viscous oil); ^{1}H NMR (500 MHz, chloroform-*d*, 298 K): δ = 7.134−7.125 (m, 32 H), 7.095−7.050 (m, 8 H), 6.590 (d, J = 2, 16 H), 6.502 (t, J = 2, 8 H), 4.695 (s, 16 H), 1.072 (s, 72 H); ^{1}H NMR (500 MHz, chloroform-*d*, 260 K): δ = 7.162−7.124 (m, 32 H), 7.090−7.050 (m, 8 H), 6.584 (d, J = 2, 16 H), 6.485 (t, J = 1−2, 8 H), 4.699 (s, 16 H), 1.061 (s, 72 H); ^{13}C NMR (125 MHz, chloroform-*d*): δ = 152.3, 148.7, 139.7, 128.3, 126.63, 126.40, 111.3, 110.2, 56.8, 34.8, 31.2; IR (ZnSe, cm^{-1}): 1575 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 200−2050, deviation from the formula) at 1898.2179 ([M + 1]$^+$, 100, −0.3 ppm for $^{13}C_1{}^{12}C_{135}{}^1H_{152}{}^{14}N_8$), 1897.2148 ([M]$^+$, 82, 0.4 ppm for $^{12}C_{136}{}^1H_{152}{}^{14}N_8$).

Decaazacyclophane 1-[N10]Bn. White crystals from benzene/isopropyl alcohol. Mp 205−207 °C; ^{1}H NMR (500 MHz, chloroform-

(55) *SAINT 6.1*; Bruker Analytical X-Ray Systems: Madison, WI, 2001.
(56) Blessing, R. *SADABS*. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1995**, *51*, 33−38.
(57) Altomare, A.; Cascarno, G.; Giacovazzo, C.; Gualardi, A. *SIR-92*. *J. Appl. Crystallogr.* **1993**, *26*, 343−350.
(58) *SHELXL-97*; Bruker Analytical X-Ray Systems: Madison, WI, 2001.

d): δ = 7.14−7.05 (m, 50 H), 6.609 (d, J = 2, 20 H), 6.474 (t, J = 2, 10 H), 4.667 (s, 20 H), 1.075 (s, 90 H); ^{13}C NMR (125 MHz, chloroform-*d*, LB = 1, 5, 10 Hz): δ = 152.2, 148.7, 139.7, 128.3, 126.68, 126.40, 111.5, 110.1, 56.8, 34.8, 31.3; IR (ZnSe, cm^{-1}): 1576 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 550−4000, deviation from the formula) at 2372.5202 ([M + 1]$^+$, 100, 0.3 ppm for $^{13}C_1{}^{12}C_{169}{}^{1}H_{190}{}^{14}N_{10}$), 2371.5132 ([M]$^+$ 75, −0.1 ppm for $^{13}C_1{}^{12}C_{169}{}^{1}H_{189}{}^{14}N_{10}$ and 1.8 ppm for $^{12}C_{170}{}^{1}H_{190}{}^{14}N_{10}$). ESI MS (Figures S12A−C, Supporting Information).

Dodecaazacyclophane 1-[N12]Bn. Treated with methanol twice (centrifuge and decantation). ^{1}H NMR (500 MHz, chloroform-*d*): δ = 7.127 (d, J = 4, 32 H), 7.15−7.05 (m, 60 H), 6.615 (d, J = 2, 24 H), 6.478 (t, J = 2, 12 H), 4.664 (s, 24 H), 1.077 (s, 108 H). ESI MS (Figures S13A−D, Supporting Information).

Tetraazacyclophane 1-[N4]H. Pale red solid, 24.0 mg (77%), 87.0 mg (83%). Mp 326−327 °C; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 7.068 (t, J = 2, 4 H,), 6.380 (d, J = 2, 8 H), 5.588 (s, 4 H), 1.269 (s, 36 H); ^{13}C NMR (125 MHz, chloroform-*d*): δ = 154.1, 144.0, 109.3, 103.3, 34.5, 31.2; IR (ZnSe, cm^{-1}): 3389 (NH), 1590 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 200−750, deviation from the formula) at 589.4230 ([M + 1]$^+$, 76, 0.7 ppm for $^{13}C_1{}^{12}C_{39}{}^{1}H_{52}{}^{14}N_4$), 588.4175 ([M]$^+$, 100, 2.9 ppm for $^{12}C_{40}{}^{1}H_{52}{}^{14}N_4$).

Hexaazacyclophane 1-[N6]H. Purple crystals, 7.5 mg (77%). Mp 396−398 °C; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 6.888 (t, J = 2, 6 H,), 6.547 (d, J = 2.0, 12 H), 5.696 (s, 6 H), 1.253 (s, 54 H); ^{13}C NMR (125 MHz, chloroform-*d*): δ = 153.6, 144.0, 142.3 (instrument artifact), 108.9, 104.8, 34.7, 31.2; IR (ZnSe, cm^{-1}): 3390 (NH), 1585 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 200−1200, deviation from the formula) at 883.6322 ([M + 1]$^+$, 89, 0.0 ppm for $^{13}C_1{}^{12}C_{59}{}^{1}H_{78}{}^{14}N_6$), 882.6276 ([M]$^+$, 100, 1.3 ppm for $^{12}C_{60}{}^{1}H_{78}{}^{14}N_6$).

Octaazacyclophane 1-[N8]H. 3.1 mg (2.6% for two steps). ^{1}H NMR (500 MHz, chloroform-*d*): δ = 6.623 (t, J = 2, 8 H,), 6.606 (d, J = 2.0, 16 H), 5.641 (s, 8 H), 1.231 (s, 72 H); IR (ZnSe, cm^{-1}): 3384 (NH), 1582 (Ar); LR-HR-FAB MS (3-NBA) cluster, *m*/*z* (ion type, % RA for *m*/*z* 200−4000, deviation from the formula) at 1177.8425 ([M + 1]$^+$, 93.7, 0.7 ppm for $^{13}C_1{}^{12}C_{79}{}^{1}H_{104}{}^{14}N_8$), 1176.8364 ([M]$^+$, 100, 1.7 ppm for $^{12}C_{80}{}^{1}H_{104}{}^{14}N_8$).

Acknowledgment. This research was supported by the National Science Foundation (CHE-0107241 and CHE-0414936). We thank Prof. Hans J. Reich (University of Wisconsin, Madison) for kindly providing the computer program WINDNMR for DNMR simulations. MS analyses were carried out at the Nebraska Center for Mass Spectrometry. We thank Drs. Ronald L. Cerny and Kurt Wulser for assistance with ESI MS experiments.

Supporting Information Available: Complete description of experimental details and product characterization, including analyses of crude reaction mixtures, dynamic NMR studies, and X-ray crystallographic files. This material is available free of charge via the Internet at http://pubs.acs.org.

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