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Monofunctionalized Pillar[5]arene as a Host for Alkanediamines

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Supporting Information

ABSTRACT: Alkanediamines serve as neutral guests for the recently discovered host pillar[5]arene. The proposed [2]pseudorotaxane nature of the superstructure of the 1:1 host−guest complexes is supported by the template-directed synthesis of a related [2]rotaxane. A synthetic route to monofunctional pillar[5]arenes has also been developed, allowing for the creation of a fluorescent sensor for alkylamine binding. The precursors to this host could act as starting points for a large library of monofunctional pillar[5]arene macrocycles.

Supramolecular chemists have extensively studied the host−guest chemistry[1] of macrocycles such as cyclodextrins,[2] crown ethers,[3] calixarenes,[4] and cucurbiturils.[5] An important application of these macrocyclic hosts is their ability to bind to, and often to act as sensors for, a variety of guests (analytes), including metal and organic cations,[6] neutral molecules,[7] anions,[8] and biomolecules.[9]

Pillar[5]arene, first reported by Ogoshi et al.[10] in 2008, is the product of the condensation of 1,4-dimethoxybenzene and formaldehyde in the presence of the Lewis acid $BF_3 \cdot OEt_2$. The hydroquinone units of this macrocycle are connected by methylene bridges in the para positions of the benzene rings, affording a D_5-symmetric structure with an overall cylindrical or pillarlike shape. Pillar[5]arene and its derivatives have been shown[11] to act as good hosts for viologens. The stabilization of these host−guest complexes can be attributed[10] to charge-transfer interactions occurring between the electron-rich cavities inside the macrocycles and the encircled electron-poor viologens. The construction of pseudorotaxanes and [*n*]rotaxanes from polyviologen threads and pillar[5]arene macrocycles using these interactions has been reported.[11d,12]

Despite extensive research[11] on the interactions between viologens and pillar[5]arenes, only a minimal effort[13] has been invested to date in studying the affinities of other small-molecule guests for this new host. On the basis of their affinities for cucurbit[6]uril,[5a] a well-studied host with a similar structure and shape, we speculated that alkylamines and alkanediamines might be ideal guests for pillar[5]arenes.

Aliphatic amines are widely used in industry (e.g., hexamethylenediamine is produced on the million ton scale annually and used in the production of nylon-6,6) and known to be slightly toxic.[14] Tuaminoheptane and methylhexanamine are stimulants banned by the World Anti-Doping Agency.[15] Identification of these compounds has largely been performed using mass spectrometry.[16] For these and other reasons, we decided to investigate the ability of pillar[5]arenes to both encapsulate and detect the presence of alkanediamines in aqueous solution.

We first investigated the ability of alkanediamines to form 1:1 complexes with 1,4-dimethoxypillar[5]arene (DMpillar[5]arene).[10] Host−guest complexation was assessed by ^{1}H NMR titration of DMpillar[5]arene into a 15 mM solution of 1,8-diaminooctane in $CDCl_3$ (Figure 1). Addition of 4.0 equiv of the host resulted in upfield shifts of 0.7 ppm for

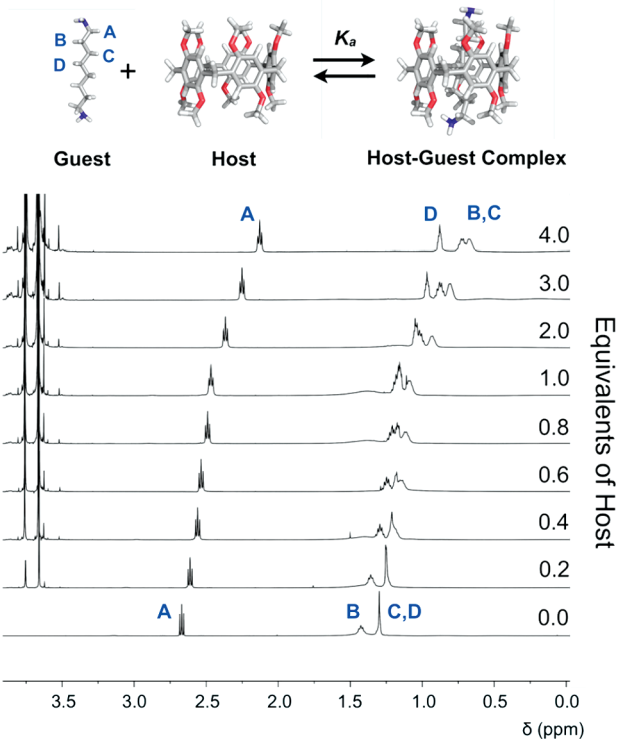


Figure 1. ^{1}H NMR titration (500 MHz, $CDCl_3$, 298 K) of DMpillar[5]arene into a 15 mM solution of 1,8-diaminooctane in $CDCl_3$. Complexation with the electron-rich cavity of DMpillar[5]arene (host) causes the protons of 1,8-diaminooctane (guest) to shift upfield. A K_a value of 70 ± 10 M^{-1} was calculated for the complex.

Received: December 19, 2010
Published: March 28, 2011

dx.doi.org/10.1021/ja111418j | *J. Am. Chem. Soc.* 2011, 133, 5668–5671

the H_B protons of the guest. An association constant (K_a) of 70 ± 10 M^{-1} in this nonpolar solvent[17] was calculated using curve-fitting analysis [see the Supporting Information (SI)]. The uncharged aliphatic guest had no significant impact on the observed chemical shifts of the host protons. Binding of *n*-octylamine in the cavity of DMpillar[5]arene was also probed by a ^{1}H NMR titration, and a K_a value of 20 ± 2 M^{-1} was obtained (see the SI).[18] Investigations of the host−guest complexation between DMpillar[5]arene and both 1,8-diaminooctane and *n*-octylamine employing Job plots (see the SI) indicated the formation of 1:1 complexes believed to be of a pseudorotaxane type[19] (i.e., with the guest threaded through the host cavity).

We synthesized a [2]rotaxane from the host−guest complex formed between DMpillar[5]arene and 1,8-diaminooctane by reacting the primary amino groups of the guest with 3,5-di-*tert*-butylbenzaldehyde. Subsequent reduction (Scheme S1 in SI) of the diimine with $NaBH_4$ in THF gave the [2]rotaxane **2** in 7% yield.[20] Even though this template-directed synthesis lacks efficiency at this time, all of the reactants, except for DMpillar[5]arene, are commercially available, rendering the [2]rotaxane an easily attainable mechanically interlocked molecule (MIM). The ^{1}H NMR spectrum (Figure 2) of **2** reveals dramatic upfield shifts for the centrally located methylene groups on the dumbbell component of DMpillar[5]arene (e.g., the proton H_D resonance is at −1.2 ppm) compared with those for the free dumbbell **1**. The synthesis and characterization of the [2]rotaxane **2** is a first step in the production of a wide range of MIMs in which pillar[5]arenes serve as the ring compounds. It also implies the formation of a 1:1 complex of a [2]pseudorotaxane nature as a precursor to the [2]rotaxane.

Having confirmed the pseudorotaxane nature of the host−guest complex, we sought to prepare a substituted pillar[5]arene capable of sensing the presence of the guest. Monofunctionalization of macrocycles is a known strategy[21] for incorporating sensor capabilities without significantly altering the binding ability of the host. We devised a synthetic approach (Scheme 1) wherein a mixture of two monomers affords a monofunctionalized pillar[5]arene (Figure 3)[22] onto which an azide moiety can subsequently be installed, allowing further functionalization with a fluorophore using the Huisgen-type[23] copper(I)-catalyzed 1,3-dipolar azide−alkyne cycloaddition (CuAAC).

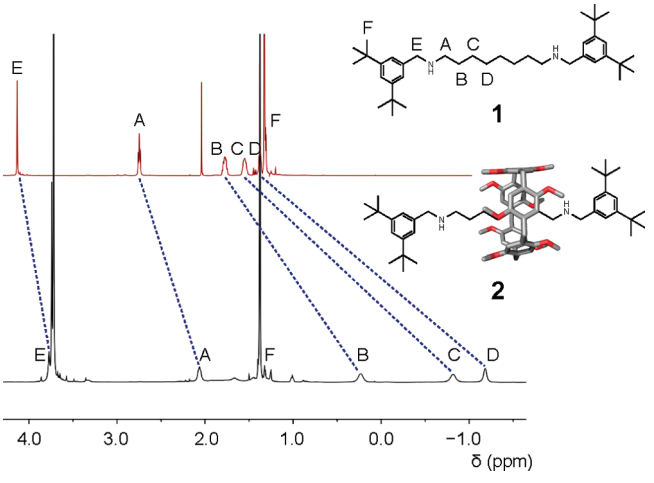
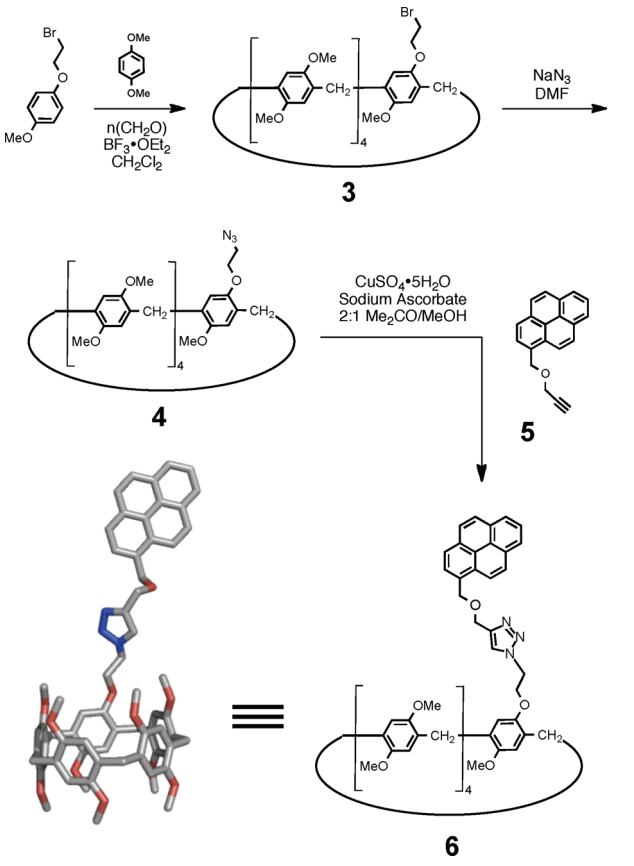


Figure 2. Comparison of the ^{1}H NMR spectra ($CDCl_3$, 500 MHz, 15 mM, 298 K) of dumbbell **1** and [2]rotaxane **2** containing pillar[5]arene. Because of shielding caused by DMpillar[5]arene, the inner aliphatic region of **1** is shifted upfield to the extent that protons C and D exhibit negative chemical shifts.

Scheme 1. Synthesis of Pyrene-Functionalized Pillar[5]arene 6; The Energy-Minimized Structure (MMFF94) of 6 Is Also Shown (H Atoms Have Been Omitted for Clarity)



Employing this strategy (Scheme 1), we obtained the monofunctionalized pillar[5]arene **3** by condensation of 5.0 equiv[24] of 1,4-dimethoxybenzene with 1.0 equiv of the unsymmetrical hydroquinone derivative 1-(2-bromoethoxy)-4-methoxybenzene[25] and 5.0 equiv of paraformaldehyde in the presence of $BF_3 \cdot OEt_2$. The Br on **3** was substituted with an azide group, creating pillar[5]arene derivative **4**, which can be functionalized through CuAAC. This example is the first involving a pillar[5]arene substituted with a functional group at a single position and able to undergo further reaction. Since CuAAC is high-yielding, functional-group-tolerant, and compatible with a wide range of substrates,[26] **4** can serve as a general precursor for a whole array of substituted pillar[5]arenes.

Primary amines are well-known[27] to quench fluorescence through photoinduced electron transfer (PET). In order to detect alkylamines and alkanediamines at low concentrations

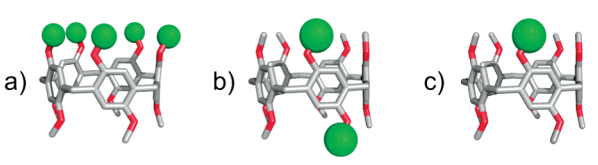


Figure 3. Models of three types of nonsymmetric pillar[5]arenes: (a) differentiated-rim pillar[5]arene; (b) copillar[5]arene, where one hydroquinone unit is different from the other four; c) monofunctional pillar[5]arene. Green spheres represent generic functional groups; H atoms have been omitted for clarity.

dx.doi.org/10.1021/ja111418j |*J. Am. Chem. Soc.* 2011, 133, 5668–5671

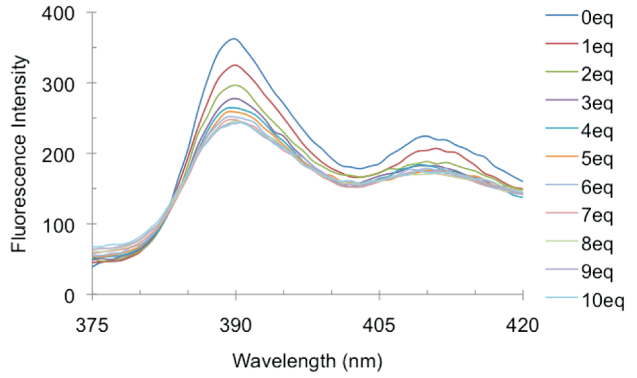
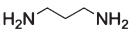
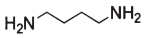
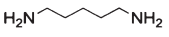
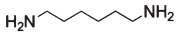
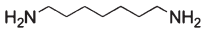
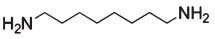
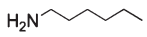
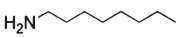
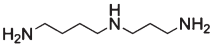
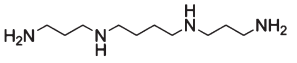


Figure 4. Fluorescence quenching experiment (57.2 μM, 1:1 MeCN/H_2O, λ_{ex} = 355 nm, λ_{em} = 395 nm). The fluorescence of **6** (57.2 μM, 1:1 MeCN/H_2O, λ_{ex} = 355 nm) was followed as 1,5-diaminopentane was titrated into the solution.

by fluorescence, we chose to react the alkyne-substituted 1-pyrenemethanol derivative **5** with **4** to give the monofunctional pillar[5]arene **6**. Since this derivative can be dissolved in 1:1 (v/v) MeCN/H_2O at the low concentration required for fluorescence spectroscopy, titrations with various alkylamines and alkanediamines into a solution of **6** in the highly polar solvent could be followed by fluorescence spectroscopy.

The quenching of fluorescence (Figure 4) was found to be significant enough that we could measure quantitatively (Table 1) the K_a values for a wide range of 1:1 complexes formed with **6**. The association constants for the series of alkanediamines containing three to eight carbon atoms are all in the vicinity of 10^4 M^{-1} and hence on the same order of magnitude as the K_a values for the formation of complexes between pillar[5]arene and viologen salts reported by Ogoshi et al.[10] Once again, the existence of 1:1 complexes was confirmed by making a Job plot with 1,8-diaminooctane (see the SI). The large difference between these K_a values and those observed for DMpillar[5]arene and 1,8-diaminooctane by ^{1}H NMR titration is attributed to the very different solvent polarities of $CDCl_3$ and aqueous MeCN as well as the significant role that hydrophobic interactions play in the complexation of **6** with its guests.

Table 1. Association Constants for 6 and Alkylamines Calculated from Fluorescence Quenching Experiments[a]

Alkylamine	Structural Formula	K_a (10^4 M^{-1})
1,3-Diaminopropane		1.00 ± 0.20
1,4-Diaminobutane		1.63 ± 0.14
1,5-Diaminopentane		2.12 ± 0.10
1,6-Diaminohexane		1.15 ± 0.14
1,7-Diaminoheptane		1.91 ± 0.10
1,8-Diaminooctane		3.60 ± 0.26
n-Hexylamine		0.29 ± 0.03
n-Octylamine		1.60 ± 0.16
Spermidine		1.86 ± 0.80
Spermine		1.02 ± 0.90

[a] Fluorescence measurement conditions: 57.2 μM, 1:1 MeCN/H_2O, λ_{ex} = 355 nm. K_a values were calculated using curve-fitting analysis software (see the SI).

Alkylamines with only a single terminal amine group had a smaller effect on the fluorescence of **6**. The two possible orientations of an *n*-alkylamine inside the cavity of **6** have the terminal amino group either directed toward the pyrene residue (and hence able to quench the fluorescence) or facing away from the fluorophore (and thus unable to cause such a profound effect). The orientation issue, coupled with the loss of one amino group (relative to an alkanediamine) to interact with the oxygen atoms on the rim of **6** by means of hydrogen bonding, offers an explanation for the lower K_a values. Titrations with 1,6-hexanediol did not decrease the fluorescence of **6**, even after the addition of 5.0 equiv of diol. 1-Aminoadamantane, which is too bulky to fit inside the cavity of pillar[5]arene,[10] only decreased fluorescence to 85% of the initial intensity after addition of 5.0 equiv.

Titration of these amines into solutions of DMpillar[5]arene or pyrene employing the same conditions did not result in a reduction of fluorescence, indicating that only **6** provides both a suitable cavity for the guest and a fluorophore that can interact photochemically with the guest. The relatively strong complexes formed between the alkanediamines and pillar[5]arene are most likely the result of hydrophobic interactions between the aliphatic chain and the pillar[5]arene cavity in addition to [C−H···π] interactions.[13a] Although hydrogen bonding between the primary amino groups and the oxygen atoms on the rims of the macrocycle may also contribute to the host−guest interactions, further investigations are required to establish the mode of binding between the pillar[5]arenes and their amine and diamine guests.

In conclusion, we have discovered and evaluated the encapsulation of uncharged aliphatic amines by the recently reported macrocycle pillar[5]arene and exploited the binding motif to prepare a [2]rotaxane with pillar[5]arene as the ring component. We have also devised a synthetic strategy to prepare monofunctionalized derivatives from a single azide-functionalized compound. By installation of a fluorophore via CuAAC "click" chemistry, a sensor for alkanediamines was obtained. Future work will probe the many interactions between pillar[5]arenes and alkylamines and target the design of novel MIMs.

■ ASSOCIATED CONTENT

Supporting Information. Synthesis and characterization of all new compounds, results of NMR and fluorescence quenching experiments, and Job plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The research at Northwestern University (NU) was sponsored by the National Center for Nano Technology Research at the King Abdulaziz City for Science and Technology (KACST)

in Saudi Arabia. The authors thank Dr. Turki S. Al-Saud, Dr. Soliman H. Alkhowaiter and Dr. Mohamed B. Alfageeh of KACST for their generous support of this program of research at NU. N.L.S. thanks the National Science Foundation for a Graduate Research Fellowship.

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(17) The interaction of aliphatic amines with the cavity of DMpillar[5]arene is expected to be driven at least partially by hydrophobic forces,[13] as observed with complexes of cucurbiturils and alkylammonium salts.[5] However, the solubility of DMpillar[5]arene is low in polar solvents at the concentrations necessary to perform ^{1}H NMR spectroscopic titrations, so the initial binding studies were performed in $CDCl_3$.

(18) Under the same conditions, the chemical shifts of the inner protons of octane moved slightly upfield (0.05 ppm) upon the addition of 1.0 equiv of the host. The difference in binding of *n*-octylamine and octane with DMpillar[5]arene in $CDCl_3$ suggests that hydrogen bonding between the primary amino groups on the guest and the methoxyl groups that line the rim of the host contribute to the stabilization of the host−guest complex.

(19) The formation of pseudorotaxanes by DMpillar[5]arene and both 1,8-diaminooctane and *n*-octylamine was supported by 2D NOESY experiments (see the SI).

(20) The low yield can be attributed in part to the solvent mixture [4:1 (v/v) THF/H_2O] used in the [2]rotaxane synthesis. This mixed solvent system was expected to support complexation between 1,8-diaminooctane and DMpillar[5]arene (the [2]rotaxane was not detected when the synthesis was attempted in $CHCl_3$), despite its having a negative influence on imine bond formation during the template-directed synthesis of the [2]rotaxane.

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