A Convergent Synthesis of Hexahomotriazacalix[3]arene Macrocycles

Panadda Chirakul,† Philip D. Hampton,* and Zsolt Bencze

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

phampton@unm.edu

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A new, convergent synthesis of hexahomotriazacalix[3]arenes **1a**−**e** is described. The key transformation in this synthesis involves the coupling of the triamines **4a**−**d** with 2,6-bis-(chloromethyl)-4-methylphenol **5** and results in the formation of the hexahomotriazacalix[3]arenes **1a**−**d** in 90−95% yield. The triamines **4a**−**d** were constructed by the one-pot reaction of monochloroaldehyde **3** and a primary amine followed by reduction to yield the triamines **4a**−**d** in 50−55% yield. Deallylation of macrocycle **1d** was accomplished by palladium catalysis to obtain the *N*-unsubstituted macrocycle **1e**, which has the potential to be a precursor to a variety of *N*-substituted hexahomotriazacalix[3]arenes.

Introduction

Calixarenes and related macrocycles have received considerable attention in recent years from many research groups as host molecules in host−guest chemistry.[1−3] Our interest in the synthesis of the hexahomotriazacalix[3]arenes **1**, abbreviated to azacalix[3]arenes in this paper, is due to their potential of being hosts for the binding of metal ions and alkylammonium ions.[3−5] The structure of the azacalix[3]arene macrocycles is shown in Figure 1. The C_3 symmetric arrangement of hydrogen-bond acceptors present in the cup of the azacalix[3]arene macrocycles resembles the structure of 1,7,13-triaza-18-crown-6 which has been reported by Lehn to complex ammonium and alkylammonium ions more strongly than alkali metal ions.[6] We have previously reported that azacalix[3]arene **1i** binds trivalent metal ions (Sc, Y, La) with the macrocycle acting as either a neutral or trianionic ligand to the metal center.[3] Takemura and Vicens and their co-workers recently reported the binding of Nd(III) by azacalix[3]arene **1h**.[4]

Previous reports of the synthesis of the azacalix[3]arene macrocycles **1** utilized a cyclooligomerization approach.[2,4,5] Takemura and co-workers reported that azacalix[3]arenes **1a**, **1b**, and **1f**−**h** could be prepared by the thermal condensation of 2,6-bis(hydroxymethyl)-phenols with primary amines.[4,5] In our hands, these conditions led to mixtures of azacalix[3]arene **1** and azacalix[4]arene **2** (Figure 1) macrocycles. We previously reported the synthesis of azacalix[3]arene **1i** by the reaction of glycine methyl ester hydrochloride with 2,6-bis(chloromethyl)-4-methylphenol.[2] This reaction results in a mixture of azacalix[3]arene **1i** and azacalix[4]arene **2i** (6:1 ratio) which could be separated by crystallization to provide pure **1i** in 19% yield. Our interest in the synthesis of the azacalix[3]arenes for host−guest and metal-ion binding studies, coupled with the low yields and the difficult separation of macrocycles **1** and **2**, led us to examine a convergent approach to the synthesis of the azacalix[3]arene macrocycles.

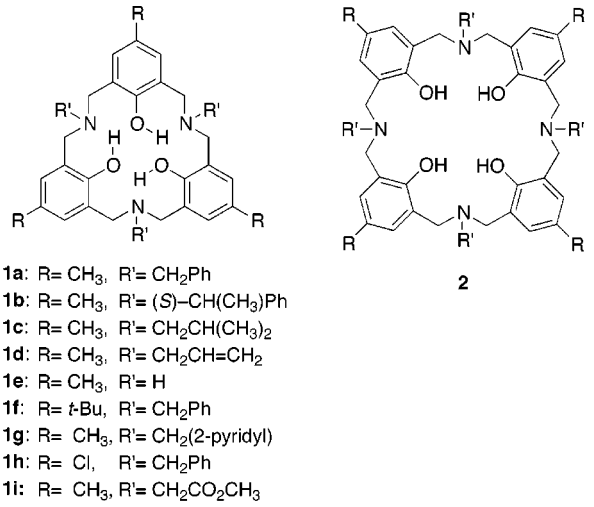

Figure 1. Structures of azacalix[3]arene **1** and azacalix[4]-arene **2** macrocycles.

In this manuscript, we report a new synthetic route, shown in Figure 2, which is efficient for the preparation of the azacalix[3]arene macrocycles **1**. This route prevents the formation of higher cyclics and allows for the synthesis of azacalix[3]arenes **1** possessing a range of *N*-substituents in high yields. An *N*-unsubstituted-azacalix-

* To whom correspondence should be addressed.

† Present address: Department of Chemistry, University of Washington, Seattle, WA 98195.

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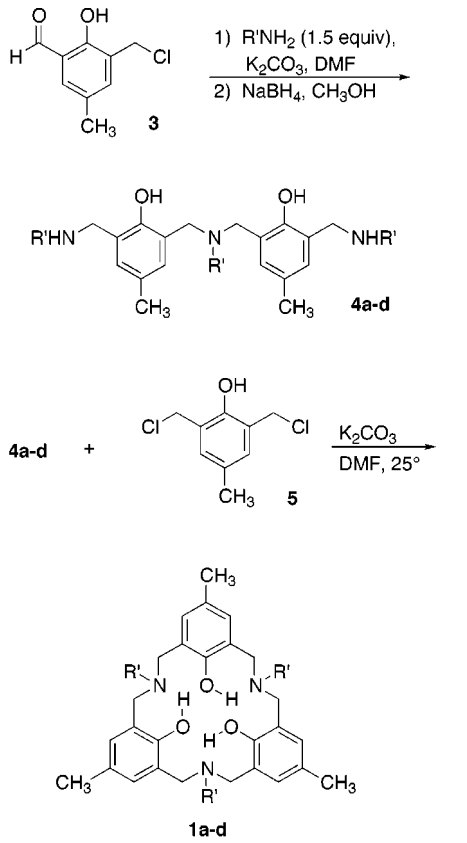

Figure 2. Convergent synthetic approach to the azacalix[3]arenes **1a**−**d**.

[3]arene **1e** has been prepared which is a versatile intermediate for the synthesis of a variety of azacalix[3]arenes having different *N*-substituents. Azacalix[3]arenes **1c**−**e** are new compounds.

Results and Discussion

Two possible convergent synthetic routes to the azacalix[3]arenes involve either (1) cyclization of an acyclic trimer or (2) condensation of a dimer with a monomer to yield the cyclic trimer **1**. Both approaches have been reported for the structurally related oxacalix[3]arene macrocycles.[7] Robson and co-workers have reported the selective synthesis of the *N*-unsubstituted azacalix[4]arene **2** (R′ = H) through the condensation of dialdehyde and diamine monomers, followed by reduction of the tetraimine macrocycle.[8] We believed that the condensation of the triamine dimers **4** with the dichloro monomer **5**, as shown in Figure 2, would be the simplest approach to the synthesis of the azacalix[3]arene macrocycles.

The triamines **4a**−**d** can be prepared by a one-pot reaction of aldehyde **3** and a primary amine in DMF at room temperature with K_2CO_3, followed by reduction with sodium borohydride (Figure 2). The yields for this step are 50−55% which are reasonable considering that a total of six separate reactions are occurring in this step: double alkylation, imine formation, and imine reduction. Only small amounts of 2,6-bis(alkylamino-methyl)-4-methylphenols are isolated (<2% yield based on starting aldehyde) as side products which result from reduction of a monoalkylated imine intermediate. The poor yields may be due to partial decomposition of aldehyde **3** in the presence of base. The air-sensitive triamines **4** were characterized by ^{1}H and ^{13}C NMR, two-dimensional NOESY experiments, and mass spectrometry.

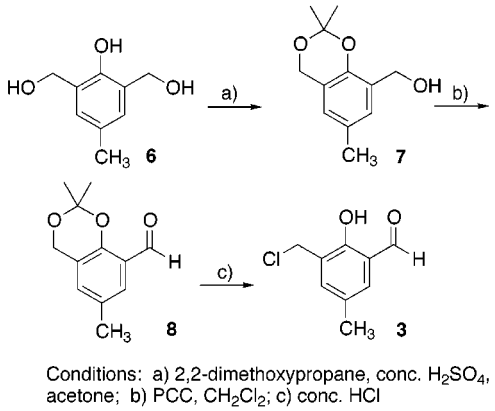

Figure 3. Preparation of aldehyde **3**.

The synthesis of the aldehyde starting material **3** was accomplished by protection of 2,6-bis(hydroxymethyl)-4-methylphenol **6** as its acetonide **7** and oxidation with pyridinium chlorochromate (PCC) to yield the protected aldehyde **8** (Figure 3).[3,9] A one-pot reaction for deprotection and chlorination of **8** with concentrated HCl resulted in the aldehyde **3** in high yield.

Coupling of the triamine dimers **4a**−**d** with 2,6-bis(chloromethyl)-4-methylphenol **5** was achieved in DMF in the presence of potassium carbonate at room temperature for 4 h to yield macrocycles **1a**−**d** in 90−95% yield. There was no evidence of the formation of higher cyclics (i.e., hexamers) or polymeric material under these conditions. We believe that the high yield for this coupling step and the absence of oligomeric or polymeric products may be due to intramolecular hydrogen-bonding which templates the cyclization of the acyclic trimer formed after monoalkylation of the triamine dimer. Azacalix[3]arenes **1a** and **1b** have previously been synthesized by Takemura and co-workers;[5] however, a number of significant differences in the chemical shifts and coupling for these compounds were noted which may suggest that their azacalix[3]arenes were contaminated with other cyclic oligomers.[10]

IR spectra of macrocycles **1a**−**e** exhibit an O−H stretching peak as a broad band in the region of 3230−3270 cm^{-1}. The low frequency of this stretch indicates

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(10) Takemura and co-workers reported (ref 5c) that compound **1a** exhibited a singlet at 7.28 ppm and a multiplet between 6.86 and 6.62 ppm for the macrocycle 3,5-arene protons in the ^{1}H NMR.; no ^{13}C NMR data were provided for this compound. In contrast, we observed a multiplet between 7.44 and 7.19 and a singlet at 6.67 ppm. For compound **1b**, Takemura and co-workers also reported (ref 5a) that the macrocycle arene protons exhibited a multiplet between 6.87 and 6.68 ppm, a singlet at 3.80 ppm for the side chain methine, and a singlet at 1.48 ppm for the side chain methyl group. We observed a singlet at 6.67 ppm, a quartet at 4.12 ppm, and a doublet at 1.62 ppm for the same signals. The multiplet for the macrocycle 3,5-arene protons in both compounds prepared by Takemura and co-workers suggests a mixture of oligomers were isolated. Both compounds exhibited singlets for these protons when they were prepared by the convergent approach discussed in this paper.

strong intramolecular hydrogen-bonding between the phenol groups and the nitrogens in the center of the macrocycle, which is consistent with the small O (phenol)−N distance in the crystal structure of azacalix[3]arene **1i**.[2] ^{1}H NMR spectra of azacalix[3]arenes **1a**−**d** exhibit singlets for the aromatic protons, the *p*-methyl groups, and the methylene groups in the macrocycle ring. When the temperature was lowered to 210 K, broadening of the methylene proton peaks in the macrocycle ring was observed for azacalix[3]arenes **1a**−**d**. In addition, the methylene signal for the benzyl groups in **1a** also exhibited broadening as the temperature was lowered. These observations can be explained by rapid nitrogen inversion and interconversion of the cone and partial-cone isomers of macrocycles **1a**−**d** on the NMR time scale at room temperature.

Deallylation of **1d** was readily achieved at room temperature in 1 h by treatment of **1d** with 2-mercaptobenzoic acid in tetrahydrofuran in the presence of 0.05 molar equivalents (per allyl group) of the preformed catalyst consisting of a 1:1 molar mixture of tris(dibenzylideneacetone)dipalladium(0) and diphenylphosphinobutane.[11] After purification by recrystallization from ethyl acetate, the *N*-unsubstituted-azacalix[3]arene **1e** was obtained in 90% yield.

Conclusion

This convergent synthetic route provides a convenient synthesis of the azacalix[3]arene macrocycles **1** with a variety of *N*-substituents and without contamination by the azacalix[4]arene macrocycles **2**. The synthesis and coupling of the triamine-dimers **4** tolerates a wide range of nitrogen substituents and could be performed on a large scale. The *N*-unsubstituted macrocycle **1e** could be easily modified through alkylation, Michael addition, or reductive amination to yield a wide range of substituted azacalix[3]arenes. We are currently examining the role of the *N*-substituent on the host−guest chemistry and metal-ion binding affinity of the azacalix[3]arene macrocycles **1**.

Experimental Section

General Procedures. *N*,*N*-Dimethylformamide (DMF) was dried over calcium sulfate or type 3 Å molecular sieve for 72 h, followed by distillation under reduced pressure and was stored over 4 Å molecular sieves. All reactions were run under N_2 atmosphere unless otherwise noted. Flash column chromatography was carried out with EM type 60 (230−400 mesh) silica gel. All compounds were pure based on TLC analysis. Elemental analyses were not performed on the triamines **4** or azacalix[3]arene **1e** due to their rapid oxidation in air. Azacalix[3]arenes **1a** and **1b** are known compounds.[5] ^{1}H NMR and ^{13}C NMR were recorded for $CDCl_3$ solutions. High resolution (HRMS) FAB mass spectra were provided by the Nebraska Center for Mass Spectrometry, University of Nebraska, in Lincoln NE.

A General Procedure for the Synthesis of the Triamine Dimers 4a−d. Synthesis of *N*-Benzyl-triamine (4a). A mixture of 2-chloromethyl-5-methylbenzaldehyde **3** (0.400 g, 2.17 mmol), benzylamine (0.24 mL, 2.2 mmol), and potassium carbonate (1.0 g, 6.5 mmol) in DMF (30 mL) was stirred for 15 min at room temperature. This reaction mixture was added dropwise to a solution of benzylamine (0.12 mL, 1.1 mmol) in DMF (20 mL) over 4 h. After complete addition, the reaction was stirred at room temperature for 24 h. Sodium borohydride (0.22 g, 5.8 mmol) in methanol (20 mL) was then added dropwise to this mixture. After stirring for 24 h, the mixture was acidified by the addition of 6 M HCl and refluxed for 4 h. The reaction mixture was evaporated to dryness, and the residue was neutralized with 1 M NaOH. Dichloromethane (25 mL) was then added to this residue, the CH_2Cl_2 layer was washed with water and dried over sodium sulfate, and the solvent was removed in vacuo. The yellow-brown solid was purified by flash column chromatography on silica gel with ethyl acetate as the eluent to give **4a** in 55% yield as a pale yellow solid. ^{1}H NMR (500 MHz) 7.30−7.20 (m, 15H), 6.79, 6.74 (pair brs, 4H), 3.80 (s, 4H), 3.70 (s, 6H), 3.63 (s, 4H), 2.16 (s, 6H); ^{13}C NMR (125 MHz) 154.1, 139.5, 137.4, 129.7, 129.6, 129.0, 128.4, 128.2, 127.5, 127.2, 127.0, 124.0, 122.9, 58.3, 54.4, 52.8, 50.5, 20.4; HRMS calcd *m*/*z* for $C_{39}H_{43}N_3O_2$ $(M + H)^+$ 586.3434, found 586.3346.

Synthesis of *N*-(S)-(−)-α-Methylbenzyl-triamine (4b). The crude product was separated by flash chromatography on silica gel with hexane/ethyl acetate (4:1) to give **4b** in 59% yield as a pale yellow solid. ^{1}H NMR (500 MHz) 7.30−7.18 (m, 15H), 6.72, 6.62 (s each, 2H each), 4.03 (q, $J = 6.8$ Hz, 1H), 3.74 and 3.70 (d, $J = 13.6$ Hz, and q, $J = 6.6$ Hz, 4H total), 3.64, 3.53 (pair d, $J = 13.4$ Hz, 2H each), 3.35 (d, $J = 13.5$ Hz, 2H), 2.12 (s, 6H), 1.50 (d, $J = 7.0$ Hz, 3H), 1.31 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (125 MHz) 154.2, 139.7, 129.6, 128.8, 128.7, 128.5, 128.1, 127.6, 127.3, 127.1, 126.7, 123.2, 57.0, 50.0, 48.8, 23.7, 20.5; HRMS calcd *m*/*z* for $C_{42}H_{49}N_3O_2$ $(M + H)^+$ 628.3825, found 628.3917; $[\alpha]^{25}_D = -67.2$ (*c* 1.5, CH_2Cl_2, optical purity unknown).

Synthesis of *N*-Isobutyl-triamine (4c). The crude product was separated by flash chromatography on silica gel with hexane/ethyl acetate (2:1) to give **4c** in 50% yield as a pale yellow solid. ^{1}H NMR (250 MHz) 6.79, 6.78 (s each, 2H each), 3.81 (s, 4H), 3.59 (s, 4H), 2.43 (d, $J = 7.2$ Hz, 4 H), 2.23 (d, $J = 6.6$ Hz, 2H), 2.19 (s, 6H), 1.98 (m, 1H), 1.77 (m, 2H), 0.90 (d, $J = 6.7$ Hz, 12H), 0.86 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (125 MHz) 154.1, 129.7, 128.7, 127.3, 124.2, 123.1, 63.0, 57.0, 55.2, 51.4, 28.2, 25.7, 21.0, 20.6, 20.5; HRMS calcd *m*/*z* for $C_{30}H_{49}N_3O_2$ $(M + H)^+$ 484.3825, found 484.3892.

Synthesis of *N*-Allyl-triamine (4d). The crude product was separated by flash chromatography on silica gel with hexane/ethyl acetate (3:1) to give **4d** in 53% yield as a pale yellow solid. ^{1}H NMR (250 MHz) 6.81 (s, 4H), 5.98−5.88 (m, 3H), 5.23−5.10 (m, 6H), 3.85 (s, 4H), 3.68 (s, 4H), 3.26 (d, $J = 8.4$ Hz, 4H), 3.13 (d, $J = 6.7$ Hz, 2H), 2.21 (s, 6H); ^{13}C NMR (62.9 MHz) 154.3, 136.1, 133.9, 129.7, 129.0, 127.5, 124.1, 122.9, 119.0, 116.5, 55.7, 54.3, 51.2, 50.3, 20.4; HRMS calcd *m*/*z* for $C_{27}H_{37}N_3O_2$, calcd $(M + Na)^+$ 458.2783, found 458.2777.

General Syntheses of Azacalix[3]arenes 1a−d. Synthesis of *N*-Benzylazacalix[3]arene (1a). A solution of 2,6-bis(chloromethyl)-4-methylphenol (0.118 g, 0.0575 mmol) in DMF (20 mL) was added dropwise over 3 h to a vigorously stirred solution of triamine **4a** (0.261 g, 0.0445 mmol) in DMF (10 mL) in the presence of K_2CO_3 (0.070 g, 0.045 mmol), and the mixture was stirred for 24 h. The reaction mixture was concentrated on a rotary evaporator, and the residue was purified by column chromatography (SiO_2, $CHCl_3$/EtOAc = 2:1) to give the product **1a** as a pale yellow solid in 95% yield. ^{1}H NMR (500 MHz) 10.80 (brs, 3H), 7.44−7.19 (m, 15H), 6.77 (s, 6H), 3.66, 3.61 (s each, 18H), 2.21 (s, 9H); ^{13}C NMR (125 MHz) 154.7, 137.2, 130.3, 129.7, 127.9, 126.8, 123.5, 57.6, 57.0, 20.4; HRMS calcd *m*/*z* for $C_{48}H_{51}N_3O_3$ $(M + H)^+$ 718.4009, found 718.4031.

Synthesis of *N*-(*S*)-(−)-α-Methylbenzylazacalix[3]arene (1b). The crude product was separated by flash chromatography on silica gel with hexane/ethyl acetate (5:1) to give **1b** in 95% yield as a white solid. ^{1}H NMR (250 MHz) 10.75 (brs, 3H), 7.29 (brs, 15H), 6.67 (s, 6H), 4.12 (q, $J = 7.5$ Hz, 3H), 3.26 (brs, 12H), 2.14 (s, 9H), 1.62 (d, $J = 6.9$ Hz, 9H); ^{13}C NMR (62.9 MHz) 155.2, 140.0, 130.0, 128.9, 127.9, 127.1, 126.8, 123.4, 56.8, 52.7, 29.7, 20.4.; HRMS calcd. *m*/*z* for $C_{51}H_{57}N_3O_3$ $(M+H)^+$ 759.4400, found 760.4450; $[\alpha]^{25}_D = -67.9$ (*c* 0.5, $CHCl_3$, optical purity unknown).

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Synthesis of *N*-Isobutylazacalix[3]arene (1c). The crude product was separated by flash chromatography on silica gel with hexane/ethyl acetate (3:1) to give **1c** in 90% yield as a white solid. ^{1}H NMR (250 MHz) 6.71 (s, 6H), 3.54 (s, 12H), 2.25 (d, J = 7.0 Hz, 6H), 2.17 (s, 9H), 1.84 (m, 3H), 0.79 (d, J = 6.3 Hz, 18H); ^{13}C NMR (125 MHz) 154.8, 130.3, 126.8, 123.9, 122.8, 63.4, 58.0, 26.0, 21.3, 20.7; Anal. Calcd for $C_{39}H_{57}N_3O_3$: C 76.06; H, 9.23. Found: C, 75.78; H, 9.27; HRMS calcd *m*/*z* for $C_{39}H_{57}N_3O_3$ $(M + H)^+$ 616.4478, found 616.4502.

Synthesis of *N*-Allylazacalix[3]arene (1d). The crude product was separated by flash chromatography on silica gel with hexane/ethyl acetate (3:1) to give **1d** in 95% yield as a white solid. ^{1}H NMR (250 MHz) 6.76 (s, 6H), 5.98−5.88 (m, 3H), 5.07−4.91 (overlapping pair dd, 6H), 3.73 (brs, 12H), 2.91 (d, J = 6.8 Hz, 6H), 2.20 (s, 9H); ^{13}C NMR (62.9 MHz) 155.3, 130.0, 126.8, 123.7, 118.5, 112.9, 56.4, 20.4, 11.9; Anal. Calcd. for $C_{36}H_{45}N_3O_3$: C 76.15; H, 7.99; N, 7.40. Found: C, 76.42; H, 8.24: N, 6.92; FABMS *m*/*z* (rel intensity) 569.5 [$(M + H)^+$, 100], 526.4 (34), 485.3 (4), 430.2 (8), 377.3 (20), 322.2 (66), 280.1 (21), 188.2 (76), 133.1 (85); HRMS calcd. *m*/*z* for $C_{36}H_{45}N_3O_3$ $(M + H)^+$ 569.3589, found 569.3572.

Synthesis of *N*-Unsubstituted-azacalix[3]arene (1e). A mixture of tris(dibenzylideneacetone)dipalladium [$Pd(dba)_2$] (0.0075 g, 0.0082 mmol) and 1,4-bis(diphenyl)phosphinobutane (DPPB, 0.0034 g, 0.0080 mmol) in 1 mL of THF was stirred at room temperature under nitrogen for 15 min. The preformed catalyst and mercaptobenzoic acid (0.0294 g, 0.185 mmol) were added to a solution of *N*-allylazacalix[3]arene **1d** (0.0300 g, 0.0528 mmol) in 5 mL of THF, and the reaction mixture was stirred at room temperature for 1 h. The mixture was treated with 10% HCl and extracted with ethyl acetate (3 × 10 mL). The aqueous layer was made basic with 1 M NaOH and extracted with ethyl acetate (5 × 10 mL). The combined extracts were dried over sodium sulfate and concentrated in vacuo. The crude product was recrystallized from ethyl acetate to obtain product **1e** in 90% yield. ^{1}H NMR (250 MHz) 6.82 (s, 6H), 3.86 (s, 12H), 2.22 (s, 9H); ^{13}C NMR (125 MHz) 155.0, 129.2, 126.9, 124.9, 125.8, 50.8, 20.5; HRMS calcd *m*/*z* for $C_{27}H_{33}N_3O_3$ $(M + H)^+$ 448.2533, found 448.2591.

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Supporting Information Available: Experimental procedures for compounds **3**, **5**, **7**, and **8**, and characterization and spectral data for triamines **4a**−**d** and azacalix[3]arenes **1a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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