JOC*Article*

Acyclic Congener of Cucurbituril: Synthesis and Recognition Properties

Christopher A. Burnett, Dariusz Witt,† James C. Fettinger, and Lyle Isaacs*

Department of Chemistry and Biochemistry, University of Maryland, College Park, College Park, Maryland 20742.

li8@umail.umd.edu

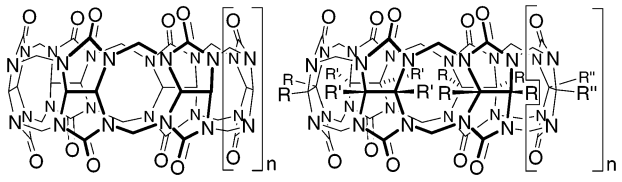
Received March 27, 2003

The cucurbit[*n*]uril (**CB**[*n*]) family of macrocycles occupies a prominent role in molecular recognition and self-assembly studies despite the current inability to access specific cucurbit[*n*]uril homologues, derivatives, and analogues by straightforward tailor-made synthetic procedures. In this paper, we explore an approach that circumvents the challenges posed by the tailor-made synthesis of macrocyclic **CB**[*n*] by preparing **1**, which functions as an acyclic CB[6] congener. The *o*-xylylene connections to the glycoluril rings preorganize **1** into the (a,a,a,a)-**1** conformation required for binding and reduce its tendency to undergo self-association. We surveyed the binding properties of **1** toward 16 amines ($K_a \leq 1.52 \times 10^4$ M^{-1}) and diol, diacid, guanidinium, and pyridinium species in pD 7.4 phosphate-buffered D_2O. We find that the recognition properties of **1** parallel those of CB[6], binding tightly to alkaneammonium species in water and exhibiting length-dependent selectivity and competitive binding with alkali metals present in solution. Compound **1** binds hexanediammonium ion only 180-fold less tightly than CB[6]. The modular synthesis of **1** suggests synthetic methods toward the preparation of acyclic CB[*n*] congeners with complex functional groups on the edges of their aromatic rings and cavity volumes similar to CB[7] and CB[8]. In combination, these results suggest that acyclic CB[*n*] congeners hold promise in molecular recognition and self-assembly studies that complements that of macrocyclic CB[*n*].

I. Introduction

Cucurbituril (CB[6]) is a macrocyclic hexamer composed of six glycoluril rings and twelve methylene bridges.[1,2] The molecular structure of CB[6] defines a hydrophobic cavity with a diameter of 5.8 Å and a volume of 164 Å^3.[3] Access to this cavity is provided by two ureidyl-carbonyl-lined portals 3.9 Å in diameter. In accord with these structural parameters, CB[6] binds to alkanediammonium ions in aqueous solution with high affinity ($K_d \approx 1$ μM) driven by the hydrophobic effect and ion−dipole interactions (Figure 1).[4] The carbonyl-lined portal also functions as a ligand for a variety of metal cations. In addition to good affinity, CB[6] exhibits high selectivity in its binding processes as a result of the rigidity of its macrocyclic structure. As a result of these outstanding recognition properties, CB[6] has been used in a variety of applications, including the catalysis of dipolar cycloadditions,[5−7] as a molecular bead in molecular necklaces and polyrotaxanes,[8,9] molecular bowls,[10] DNA complexation,[11,12] and for the removal of contaminants from aqueous waste streams.[13]

CHART 1



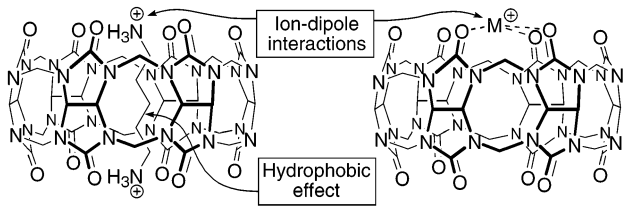


FIGURE 1. Illustration of the binding of alkanediammonium species and metal ions to CB[6].

* To whom correspondence should be addressed.

† Current address: Chemical Faculty, Technical University of Gdansk, Narutowicza 11/12, 80-952 Gdansk, Poland.

(1) Behrend, R.; Meyer, E.; Rusche, F. *Liebigs Ann. Chem.* **1905**, *339*, 1−37.

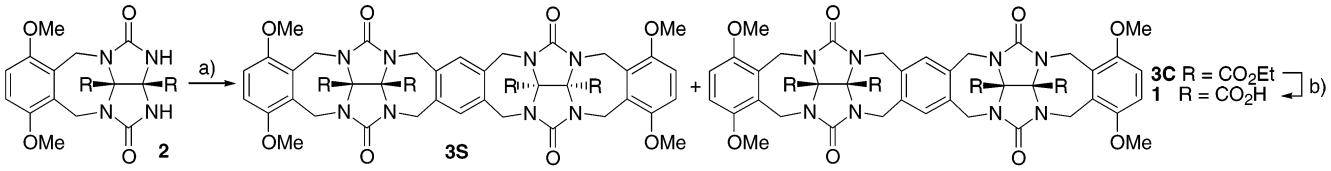
(2) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368.

(3) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540−541.

(4) (a) Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1983**, *48*, 3618−3619. (b) Mock, W. L.; Shih, N. Y. *J. Org. Chem.* **1986**, *51*, 4440−4446. (c) Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1988**, *110*, 4706−4710. (d) Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1989**, *111*, 2697−2699.

10.1021/jo034399w CCC: $25.00
Published on Web 07/08/2003

SCHEME 1. Synthesis of 1[a]



[a] Conditions: (a) DMSO, *t*-BuOK (15 min) and then $C_6H_2(CH_2Br)_4$; (b) CH_3OH, H_2O, LiOH, 80%.

Despite the wide range of applications in which CB[6] has proved to be useful, there are a number of factors that have prevented its more widespread use. For example, concentrated aqueous solutions of CB[6] can only be obtained by the addition of high concentrations of acid (e.g., HCO_2H or HCl) or salts (e.g., Na_2SO_4, KCl, CsCl, and $CaCl_2$).[4a,10] In addition, the rigid and relatively small cavity of CB[6] does not allow for the complexation of large molecular guests. To date, two lines of inquiry have been pursued to address these deficiencies. To change the size of the hydrophobic cavity, the groups of Kim and Day conducted the cucurbituril forming reactions under mild, kinetically controlled conditions that resulted in the isolation of the new cucurbituril homologues CB[5], CB[7], and CB[8].[3,14−16] More recently, Day has isolated CB[10] as its CB[5] inclusion complex (CB[5]@CB[10]).[17] To improve the solubility of cucurbiturils, the groups of Stoddart, Kim, Day, and Nakamura have reported the use of substituted glycolurils in cucurbituril-forming reactions that allowed the isolation and characterization of CB[*n*] derivatives Me_{10}CB[5], Cy_5CB[5], Cy_6CB[6], Ph_2-CB[1,5], and Me_6CB[3,3].[18−21] Both lines of inquiry require control over the formation and relative stereochemistry of the methylene-bridged glycoluril dimer substructure[22] (bold in CB[6]), which is the fundamental building block of CB[*n*] and its derivatives. Several challenges remain to be addressed before the tailor-made synthesis of CB[*n*] derivatives can be achieved.

To circumvent the challenges posed by the formation of macrocyclic CB[*n*] derivatives, we targeted the synthesis and molecular recognition properties of acyclic congeners of cucurbituril. The use of acyclic analogues of complex macrocyclic hosts can be traced back to the chemistry of podands and lariat ethers.[23,24] These acyclic hosts are not preorganized[25] and often show reductions in binding affinity of 10^4−10^5 M^{-1} compared to the related macrocycles.[26,27] In this paper, we report the synthesis of a conformationally biased acyclic CB[6] congener **1** (Scheme 1), whose recognition properties toward alkanediammonium ions parallel those of CB[6] with only moderate reductions in binding affinity.

Compound **1** bears a structural and functional similarity to several classes of hosts other than CB[6]. For example, the use of polyoxygenated molecules (crown ethers, aza crowns, and podands) as hosts for alkaneammonium, alkanediammonium, and viologens is well-known in the literature.[25,28,29] Of particular relevance to our studies is the pioneering work of Nolte, who used glycoluril-based crown ethers and aza crowns as hosts for ammonium ions and viologens.[30] In a series of elegant papers, Klärner has reported the preparation of dibenzonorbornane-based molecular tweezers and their use as hosts both for electron-deficient aromatic guests in organic solution and for N-alkylpyridinium salts in aqueous solution.[31]

II. Results and Discussion

A. Design of Compound 1. We designed **1** as an acyclic congener of cucurbituril to circumvent the syn-

(5) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619−3920.
(6) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302−5308.
(7) Tuncel, D.; Steinke, J. H. G. *Chem. Commun.* **2002**, 496−497.
(8) Whang, D.; Park, K.-M.; Heo, J.; Ashton, P.; Kim, K. *J. Am. Chem. Soc.* **1998**, *120*, 4899−4900.
(9) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96−107.
(10) Jeon, Y.-M.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790−9791.
(11) Lim, Y.-B.; Kim, T.; Lee, J. W.; Kim, S.; Kim, H.-J.; Kim, K.; Park, J. *Bioconjugate Chem.* **2002**, *13*, 1181−1185.
(12) Isobe, H.; Tomita, N.; Lee, J. W.; Kim, H.-J.; Kim, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 4257−4260.
(13) Kornmuller, A.; Karcher, S.; Jekel, M. *Water Res.* **2001**, *35*, 3317−3324.
(14) Kim, K.; Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K. Cucurbituril derivatives, their preparation and uses. European Patent Appl. EP 1 094 065 A2, 2001.
(15) Day, A. I.; Arnold, A. P.; Blanch, R. J. Method for Synthesis Cucurbiturils. PCT Intl. Appl. PCT/AU00/00412, 2000.
(16) Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094−8100.
(17) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 275−277.
(18) Flinn, A.; Hough, G. C.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1475−1477.
(19) Zhao, J.; Kim, H.-J.; Oh, J.; Kim, S.-Y.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4233−4235.
(20) Isobe, H.; Sato, S.; Nakamura, E. *Org. Lett.* **2002**, *4*, 1287−1289.
(21) (a) Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, *32*, 995−1006. (b) Smeets, J. W. H.; Sijbesma, R. P.; Niele, F. G. M.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 928−929. (c) Smeets, J. W. H.; Sijbesma, R. P.; van Dalen, L.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Org. Chem.* **1989**, *54*, 3710−3717. (d) Smeets, J. W. H.; van Dalen, L.; Kaats-Richter, V. E. M.; Nolte, R. J. M. *J. Org. Chem.* **1990**, *55*, 454−461. (e) Schenning, A. P. H. J.; de Bruin, B.; Rowan, A. E.; Kooijman, H.; Spek, A. L.; Nolte, R. J. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2132−2134. (f) Escuder, B.; Rowan, A. E.; Feiters, M. C.; Nolte, R. J. M. *Tetrahedron Lett.* **2001**, *42*, 2751−2753. (g) Thordarson, P.; Bijsterveld, E. J. A.; Elemans, J. A. A. W.; Kasák, P.; Nolte, R. J. M.; Rowan, A. E. *J. Am. Chem. Soc.* **2003**, *125*, 1186−1187.
(22) Day, A. I.; Arnold, A. P.; Blanch, R. J. *Molecules* **2003**, *8*, 74−84.
(23) (a) Chakraborty, A.; Wu, A.; Witt, D.; Lagona, J.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2002**, *124*, 8297−8306. (b) Witt, D.; Lagona, J.; Damkaci, F.; Fettinger, J. C.; Isaacs, L. *Org. Lett.* **2000**, *2*, 755−758. (c) Wu, A.; Chakraborty, A.; Witt, D.; Lagona, J.; Damkaci, F.; Ofori, M.; Chiles, K.; Fettinger, J. C.; Isaacs, L. *J. Org. Chem.* **2002**, *67*, 5817−5830.
(24) Gokel, G. W.; Murillo, O. Podands. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 1, pp 1−33.
(25) Gokel, G. W.; Schall, O. F. Lariat Ethers. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 1, pp 97−152.
(26) Cram, D. J. *Angew. Chem., Int. Ed.* **1988**, *27*, 1009−1020.
(27) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600−606.
(28) Timko, J. M.; Helgeson, R. C.; Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 7097−7099.
(29) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89−112.
(30) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348−3391.

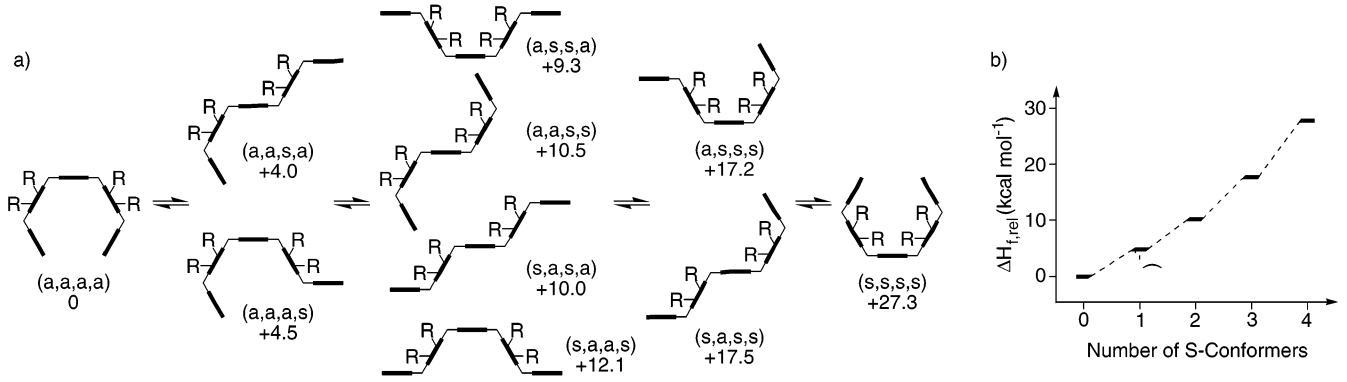


FIGURE 2. (a) Schematic representation of the possible conformations of **1** and their AM1 calculated relative heats of formation. The descriptors "a" and "s" refer to the anti or syn relationship between the xylylene rings and the carboxylic acid groups on the convex face of the molecule. R = CO_2H. (b) Plot of the relative heat of formation versus the number of syn conformations.

thetic issues that complicate CB[*n*] synthesis, namely, methylene-bridged glycoluril dimer formation and macrocyclization, while enhancing its aqueous solubility and preserving its recognition properties.[32] To enhance the solubility properties, we used glycoluril derivatives bearing CO_2Et groups that impart organic solubility and can be deprotected to the water-soluble carboxylic acid form. To preserve the recognition properties of CB[6] in an acyclic CB[6] congener requires a high degree of preorganization. We chose *o*-xylylene groups as the linking groups between glycoluril rings because this substructure was known to prefer the anti conformation,[33−35] which would result in preorganization, and because efficient synthetic protocols were available from the work of Nolte and Rebek.[36−41] These *o*-xylylene groups also obviate the need for methylene-bridged glycoluril dimer formation.

B. Synthesis of Compound 1. The synthesis of **1** is shown in Scheme 1. Deprotonation of **2**[22b] with *t*-BuOK in DMSO followed by alkylation with 1,2,4,5-tetrakis-(bromomethyl)benzene yielded S-shaped **3S** and its C-shaped diastereomer **3C**. The assignment of the relative stereochemistry of **3S** and **3C** was not possible spectroscopically. Fortunately, we were able to obtain single crystals of both diastereomers and their structures were solved by X-ray crystallography. We deprotected **3C** by treatment with LiOH and isolated the free tetracarboxylic acid by acidification with PTSA followed by washing with MeOH to remove PTSA and it salts.

C. Conformational Analysis of Compound 1. Each of the four pairs of methylene bridges of **1** can adopt two different conformations. These conformations differ in the disposition of their *o*-xylylene rings with respect to the carboxylic acid substituents on the convex face of the adjacent glycoluril rings. Following the convention of Nolte,[33] we denote these conformations as syn (s) when the conformation of the methylene bridges of the substituted *o*-xylylene ring orients the ring in the same direction as the adjacent carboxylic acid groups and anti (a) when they point in opposite directions. Figure 2a shows schematic representations of 10 different conformations of **1**. These conformations are arranged from left to right as the number of syn conformations is increased from zero to four. Figure 2b shows a plot of relative heats of formation (AM1) as a function of the number of syn conformations. The heat of formation of the (a,a,a,a)-**1** conformation is ∼4 kcal/mol lower than either of the conformations containing a single syn conformation. Conformers containing larger number of syn conformations are significantly less stable. The conformational preference of the *o*-xylylene rings were, therefore, expected to bias **1** toward the (a,a,a,a)-conformation required to act as an acyclic congener of cucurbituril.

D. X-ray Crystallographic Characterization of 3C and 3S. Figure 3 shows the structures of **3C** and **3S** in the crystal. The most unusual feature of these crystal structures is observed in the structure of **3C** (Figure 3a). Compound **3C** crystallizes in the (a,s,a,a)-**3C** conformation that is predicted to be ∼4 kcal/mol less stable than the (a,a,a,a)-conformer. We attribute this unusual result to crystal packing forces and the presence of solvating toluene rings. To the best of our knowledge, this is the first direct experimental observation of the anti confor-

(31) (a) Klärner, F.-G.; Benkoff, J.; Boese, R.; Burkert, U.; Kamieth, M.; Naatz, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1130−1133. (b) Kamieth, M.; Klärner, F.-G.; Diederich, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 3303−3306. (c) Kamieth, M.; Burkert, U.; Corbin, P. S.; Dell, S. J.; Zimmerman, S. C.; Klärner, F.-G. *Eur. J. Org. Chem.* **1999**, *2741*, 1−2749. (d) Klärner, F.-G.; Burkert, U.; Kamieth, M.; Boese, R.; Benet-Buchholz, J. *Chem. Eur. J.* **1999**, *5*, 1700−1707. (e) Klärner, F.-G.; Burkert, U.; Kamieth, M.; Boese, R. *J. Phys. Org. Chem.* **2000**, *13*, 604−611. (f) Brown, S. P.; Schaller, T.; Seelbach, U. P.; Koziol, F.; Ochsenfeld, C.; Klärner, F.-G.; Spiess, H. W. *Angew. Chem., Int. Ed.* **2001**, *40*, 717−720. (g) Klärner, F.-G.; Panitzky, J.; Bläser, D.; Boese, R. *Tetrahedron* **2001**, *57*, 3673−3687. (h) Jasper, C.; Schrader, T.; Panitzky, J.; Klärner, F.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1355−1358. (i) Ruloff, R.; Seelbach, U. P.; Merbach, A. E.; Klärner, F.-G. *J. Phys. Org. Chem.* **2002**, *15*, 189−196.

(32) Compounds with similar topological features are known to act as hosts for resorcinols in organic solution: (a) Reek, J. N. H.; Rowan, A. E.; Crossley, M. J.; Nolte, R. J. M. *J. Org. Chem.* **1999**, *64*, 6653−6663. (b) Murray, B. A.; Whelan, G. S. *Pure Appl. Chem.* **1996**, *68*, 1561−1567.

(33) Sijbesma, R. P.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1991**, *113*, 6695−6696.

(34) Sijbesma, R. P.; Wijmenga, S. S.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1992**, *114*, 9807−9813.

(35) Reek, J. N. H.; Engelkamp, H.; Rowan, A. E.; Elemans, J. A. A. W. *Chem. Eur. J.* **1998**, *4*, 716−722.

(36) Valdéz, C.; Spitz, U. P.; Toledo, L. M.; Kubik, S. W.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 12733−12745.

(37) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699−1701.

(38) O'Leary, B. M.; Szabo, T.; Svenstrup, N.; Schalley, C. A.; Luetzen, A.; Schaefer, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 11519−11533.

(39) Reek, J. N. H.; Kros, A.; Nolte, R. J. M. *Chem. Commun.* **1996**, 245−247.

(40) Elemans, J. A. A. W.; de Gelder, R.; Rowan, A. E.; Nolte, R. J. M. *Chem. Commun.* **1998**, 1553−1554.

(41) Jansen, R. J.; Rowan, A. E.; de Gelder, R.; Scheeren, H. W.; Nolte, R. J. M. *Chem. Commun.* **1998**, 121−122.

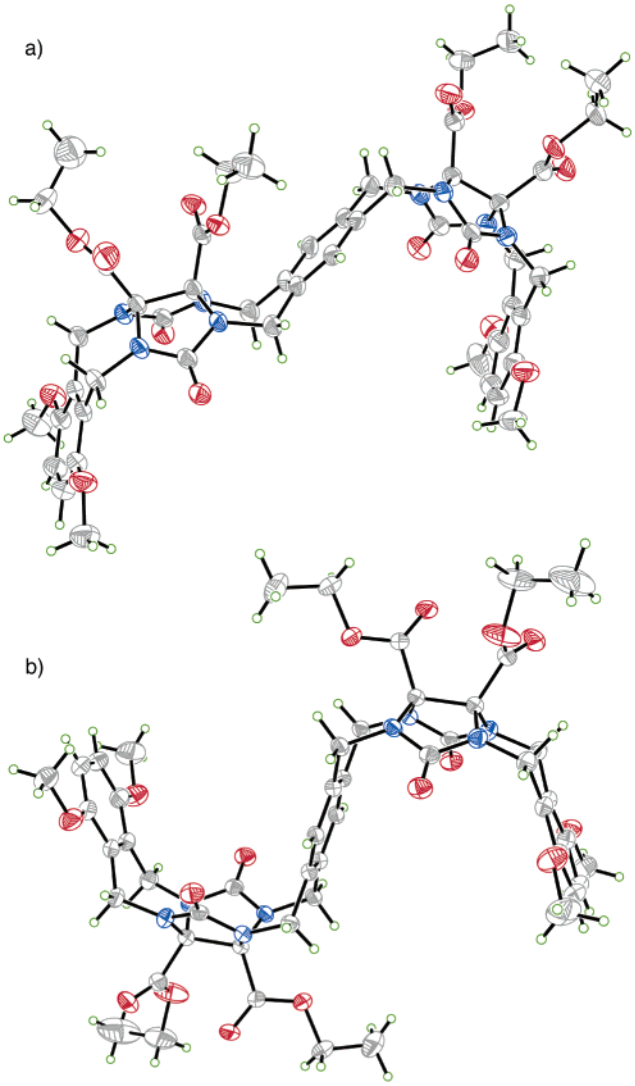


FIGURE 3. ORTEP representations of the molecular structures of: (a) **3C** and (b) **3S** in the crystal. Thermal ellipsoids are drawn at the 50% probability level. The solvating $PhCH_3$ and CH_2Cl_2 have been removed for clarity. Some of the CO_2-Et groups adopt two orientations in the crystal; here, the major orientation component is depicted. C, gray; H, green; N, blue; O, red.

mation in *o*-xylylene-substituted glycolurils.[34,35] The remaining structural features of this class of compounds are quite similar to those determined previously for compounds containing substituted glycoluril rings. The distances between the ureidyl O-atoms of each glycoluril ring are not unusual (**3C**, 5.46 and 5.66 Å; **3S**, 5.64 Å). These distances do, however, define the cavity depth of the cucurbituril congener and are smaller than those measured for CB[5] (6.17−6.22 Å) and CB[6] (5.98−6.04 Å).[2,3] Individual molecules of **3C** and **3S** dimerize in the crystal by $\pi-\pi$ interactions,[42,43] which results in discrete dimers and an infinite tape-like motif, respectively.[44,45]

E. Compound 1 is an Acyclic CB[6] Congener. The following sections compare and contrast the recognition properties of **1** and CB[6] toward ammonium, diol, diacid, guanidinium, and pyridinium species.

1. Effect of Buffer Concentration on the Self-Association of 1. Water-soluble glycoluril derivatives bearing two *o*-xylylene walls are known to undergo self-association in aqueous solution.[39,40,46−48] We studied the self-association of **1** to ensure that it would not impinge on the planned ammonium ion binding studies. Accordingly, we performed ^{1}H NMR dilution experiments in phosphate-buffered D_2O (pD 7.4) and observed the change in chemical shift of several protons as a function of the concentration of **1**. Fitting of these changes in chemical shift versus concentration[49] allowed us to determine self-association (K_s) constants of 115 ± 4 and 196 ± 19 M^{-1} in 100 and 5 mM sodium phosphate-buffered D_2O, respectively. In unbuffered D_2O, the self-association constant increases (K_s = 1127 ± 129 M^{-1}). We were not able to observe intermolecular NOEs in the **1·1** dimer that would allow us to elucidate its geometry, although the geometry seen in its crystal structure (Supporting Information, Figure S1) is a reasonable hypothesis. Our rationale for the observed decrease in K_s as the buffer concentration increases rests on the known affinity of sodium ions for the carbonyl-lined portals of CB[6] (Figure 1). We believe that the (a,a,a,a)-**1** shows similar affinity for Na^+ ions in aqueous solution, whereas (a,s,a,a)-**1** would not be expected to bind Na^+. Increasing the concentration of Na^+, therefore, sequesters increasing amounts of **1** as the (a,a,a,a)-conformer, which is not expected to undergo self-association.

2. Effect of Cation and Buffer Concentration on the Ability of 1 to Bind 1,6-Hexanediammonium Ion in Aqueous Solution. Mock and co-workers have studied the binding of mono- and diamines to CB[6] in aq HCO_2H.[4] Among the numerous amines studied, the complex between CB[6] and 1,6-hexanediamine (**4**) is one of the strongest (K_d = 0.36 μM). We therefore decided to start our investigation of the recognition properties of **1** by examining its interaction with **4** in pD 7.4 phosphate-buffered D_2O. In these experiments we fixed the concentration of **1** at 100 μM, since at this concentration greater than 96% of **1** is present as the free monomer when the phosphate buffer concentration is between 5 and 100 mM. Figure 4 shows a plot of the change in chemical shift of several protons of **1** as a function of 1,6-hexanediamine concentration. The solid line represents the best fit of these changes in chemical shift to the model governing 1:1 binding (K_a = 15200 M^{-1}; K_d = 65 μM). We confirmed the 1:1 stoichiometry by performing a Job plot that shows a clear maximum at χ(**1**) = 0.5 (Figure 5). We hypothesized above that the concentration of the buffer effects the self-association constant of **1** by sequestering it in

(42) (a) Holder, S. J.; Elemans, J. A. A. W.; Donners, J. J. J. M.; Boerakker, M. J.; de Gelder, R.; Barberá, J.; Rowan, A. E.; Nolte, R. J. M. *J. Org. Chem.* **2001**, *66*, 391−399. (b) Reek, J. N. H.; Elemans, J. A. A. W.; de Gelder, R.; Beurskens, P. T.; Rowan, A. E.; Nolte, R. J. M. *Tetrahedron* **2003**, *59*, 175−185.
(43) Wu, A.; Chakraborty, A.; Fettinger, J. C.; Flowers, R. A., II; Isaacs, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4028−4031.
(44) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383−2420.
(45) Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139−1159.
(46) Elemans, J. A. A. W.; Slangen, R. R. J.; Rowan, A. E.; Nolte, R. J. M. *J. Incl. Phenom. Macrocyclic Chem.* **2001**, *2001*, 65−68.
(47) Elemans, J. A. A. W.; Rowan, A. E.; Nolte, R. J. M. *J. Am. Chem. Soc.* **2002**, *124*, 1532−1540.
(48) (a) Isaacs, L.; Witt, D.; Fettinger, J. C. *Chem. Commun.* **1999**, 2549−2550. (b) Isaacs, L.; Witt, D.; Lagona, J. *Org. Lett.* **2001**, *3*, 3221−3224. (c) Isaacs, L.; Witt, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1905−1907.
(49) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

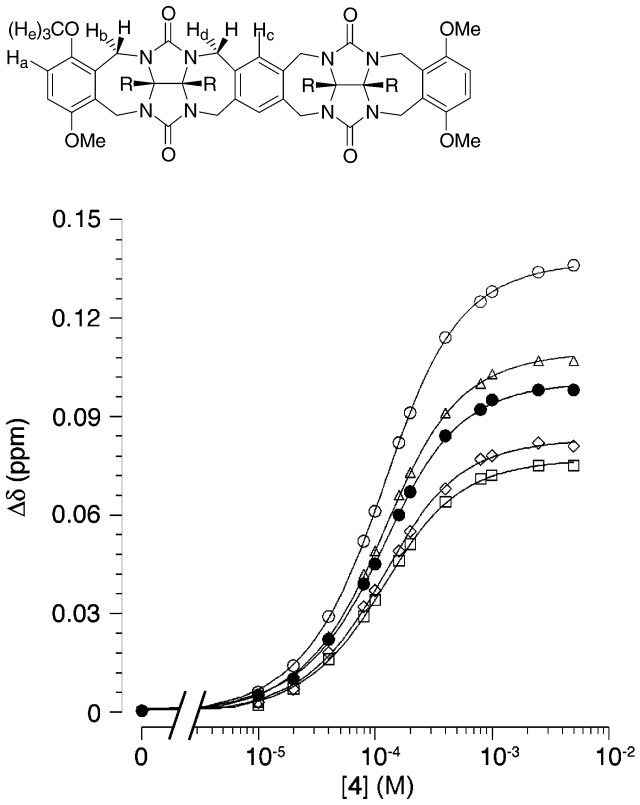
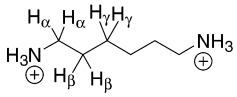


FIGURE 4. Fitting of the chemical shift versus concentration data (H_a, ○; H_b, △; H_c, ●; H_d, ◇; H_e, □). Conditions: [**1**] = 100 μM, 5 mM sodium phosphate-buffered D_2O, pD 7.4, 298 K.



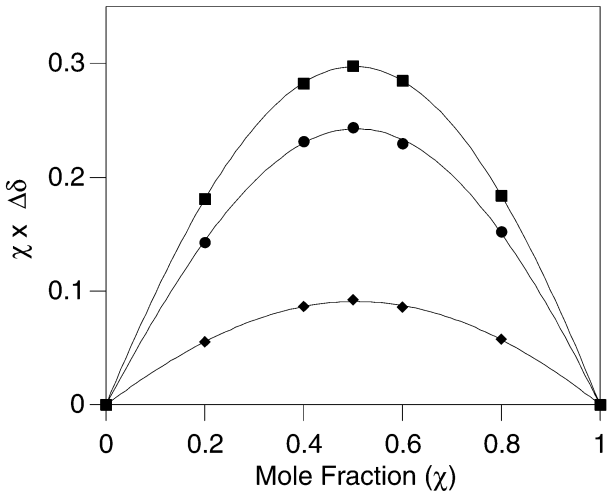


FIGURE 5. Job plot analysis of the stoichiometry of the interaction between **1** and **4**. The solid lines are intended to guide the eye. H_α, ■; H_β, ●; $H\gamma$, ◆.

its (a,a,a,a)-**1** conformer. If this hypothesis is correct, then Na^+ should compete with **4** for binding to **1**. Figure 6 shows the values of K_a measured for the interaction of **1** with **4** at different phosphate concentrations. As the phosphate buffer concentration is increased, the value of K_a decreases rapidly and reaches a value of 866 ± 40

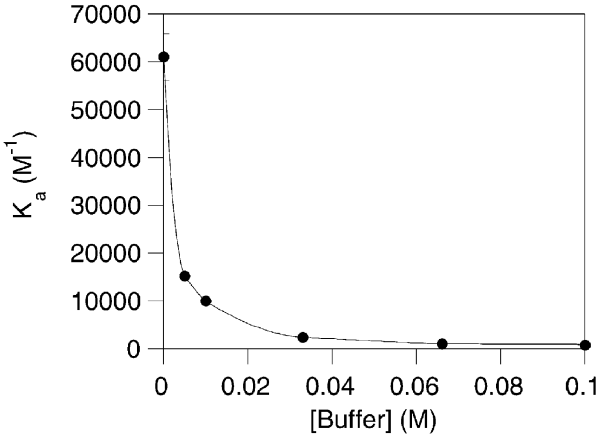


FIGURE 6. Plot of K_a versus buffer concentration (phosphate, pD 7.4) for the binding of 1,6-hexanediamine with **1**. The solid line is intended to guide the eye.

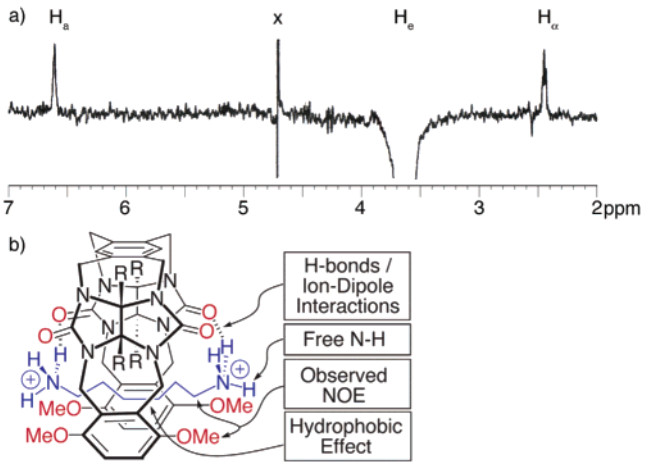
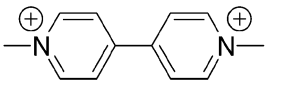


FIGURE 7. (a) Portion of the selective one-dimensional ROESY spectrum obtained for **1·4** (10 mM, 298K, 500 MHz) upon irradiation of the OCH_3 group (3.6 ppm). The resonance marked "x" arises due to incomplete suppression of residual HOD. The protons are labeled as in Figures 4 and 5. (b) Proposed geometry of the **1·4** complex.

M^{-1} in 100 mM phosphate buffer. This result suggests that **1** binds Na^+ at its carbonyl and methoxy group-lined portal in a manner similar to that of CB[6]. CB[6] is also known to interact with several other mono- and divalent cations in aqueous solution. To determine the effect of cation on the affinity of **1** for **4**, we performed titrations in 5 mM lithium and potassium phosphate buffers. In these two buffers, the values of K_a for the interaction of **1** with **4** are 20170 ± 370 and 24400 ± 500 M^{-1}, respectively.

3. Geometry of the 1·4 Complex. Figure 7b shows a line drawing of the proposed three-dimensional structure of the **1·4** complex. This structural suggestion is based on the structural similarity of **1** and CB[6], the computed conformational preferences of **1**, the 1:1 stoichiometry based on the Job plot analysis, and two additional pieces of evidence. For example, the methylene protons of the **4** experience significant complexation-induced changes in chemical shift ($\Delta\delta_{sat}$: H_α −0.64 ppm; H_β −1.70 ppm; H_γ −2.11 ppm), which suggests that these protons are in the shielding region defined by the three aromatic

TABLE 1. Thermodynamic Data for Host−Guest Complexes of Substituted Ammonium Ions with 1 and CB[6]

entry	guest	**1** K_a (M^{-1})[a]	$\Delta G°$ (kcal/mol)	CB[6] K_a (M^{-1})[b]
1	$H_2N(CH_2)_4NH_2$ (**5**)	7.24×10^2	−3.9	1.54×10^5
2	$H_2N(CH_2)_5NH_2$ (**6**)	5.96×10^3	−5.1	2.44×10^6
3	$H_2N(CH_2)_6NH_2$ (**4**)	1.52×10^4	−5.7	2.78×10^6
4	$H_2N(CH_2)_7NH_2$ (**7**)	6.46×10^3	−5.2	4.35×10^4
5	$H_2N(CH_2)_8NH_2$ (**8**)	7.06×10^3	−5.2	9.09×10^3
6	$CH_3(CH_2)_2NH_2$ (**9**)	1.05×10^2	−2.8	1.22×10^4
7	$CH_3(CH_2)_3NH_2$ (**10**)	2.60×10^2	−3.3	1.00×10^5
8	$CH_3(CH_2)_4NH_2$ (**11**)	5.56×10^2	−3.7	2.38×10^4
9	$CH_3(CH_2)_5NH_2$ (**12**)	2.20×10^2	−3.2	2.27×10^3
10	$CH_3NH(CH_2)_6NHCH_3$ (**13**)	1.22×10^4	−5.6	1.72×10^6
11	$(CH_3)_2N(CH_2)_6N(CH_3)_2$ (**14**)	4.25×10^3	−4.9	9.09×10^3
12	$(2\text{-}C_4H_3O)CH_2NH_2$ (**15**)	<10		1.14×10^5
13	$p\text{-}H_2NCH_2(C_6H_4)CH_2NH_2$ (**16**)	4.96×10^2	−3.7	nd
14	$(CH_3)_2CHCH_2NH_2$ (**17**)	1.28×10^2	−2.8	2.17×10^4
15	$(CH_3)_2CH(CH_2)_2NH_2$ (**18**)	1.24×10^2	−2.9	3.57×10^4
16	$H_2N(CH_2)_2SS(CH_2)_2NH_2$ (**19**)	7.94×10^2	−4.0	nd
17	$HO(CH_2)_6OH$ (**20**)	<10		nd
18	$HO_2C(CH_2)_4CO_2H$ (**21**)	<10		1.69×10^2 [c]
19	$H_2N(CH_2)_4NHC(NH)NH_2$ (**22**)	1.40×10^4	−5.7	nd
20	 (**23**)	2.06×10^3	−4.5	nd

[a] Conditions: 5 mM sodium phosphate-buffered D_2O (pD = 7.4); [**1**] = 100 μM, 25 °C; error bars ≤ 10%; nd = not determined. [b] Ref 4b: conditions: D_2O/85% HCO_2H (1:1, v/v), 40 °C. [c] Ref 52: conditions: H_2O/HCO_2H (1:1, v/v), 25 °C.

rings in the cavity of the (a,a,a,a)-**1** conformer. The smaller value of $\Delta\delta$ observed for H_α suggests that these protons reside at the ends of the complex in a less shielded environment near the OMe groups. We performed selective one-dimensional ROESY experiments to provide further structural information. For example, when the OCH_3 group of **1** was irradiated, we observed an intramolecular NOE to H_a and an intermolecular NOE to the α-methylene group ($C(H_\alpha)_2NH_3^+$) of the guest **4** (Figure 7a).[50] Similarly, irradiation of the α-methylene group of guest **4** leads to intramolecular NOEs with H_β and H_γ and an intermolecular NOE to H_e (not shown). These important NOEs support the geometry depicted in Figure 7 and further suggest that the OCH_3 groups may be oriented toward the center of the **1**·**4** complex.

4. Compound 1 Binds a Variety of Alkaneammonium Ions in Aqueous Solution. After establishing that **1** behaves as an acyclic congener of CB[6] in its binding behavior with **4**, we wanted to determine if **1** binds to a wide range of alkanediammonium and alkaneammonium ion in water just like CB[6] itself. Table 1 shows the binding constants (K_a) determined for the interaction of 20 guests with **1** in phosphate-buffered D_2O by ^1H NMR titrations and the corresponding values of $\Delta G°$. Table 1 also gives the values of K_a measured for their interaction with CB[6] for comparison.

a. Length-Dependent Selectivity. Compound **1**, similar to CB[6], binds tightly to alkanediammonium ions by a combination of ion−dipole interactions and the hydrophobic effect with values of $\Delta G°$ up to −5.7 kcal mol^{-1}. Table 1 shows that **1** exhibits length dependent affinity for alkanediammonium ions **4** − **8** (entries 1−5) and alkaneammonium ions **9** − **12** (entries 6−9) that is similar to CB[6] (Figure 8). Both **1** and CB[6] exhibit highest affinity for hexanediammonium ion (**4**) whose chain length matches the depth of their cavities (Figure 8a). In the alkaneammonium series (Figure 8b), **1** exhibits a preference for binding to pentylammonium ion (**11**) whereas CB[6] prefers butylammonium ion (**10**). This change in preference is probably due to the relatively hydrophobic OCH_3 groups on the rim of **1** compared to the carbonyl lined portal of CB[6]. The selectivity observed for **1** is less pronounced than for CB[6] presumably due to the greater flexibility of the acyclic host. The

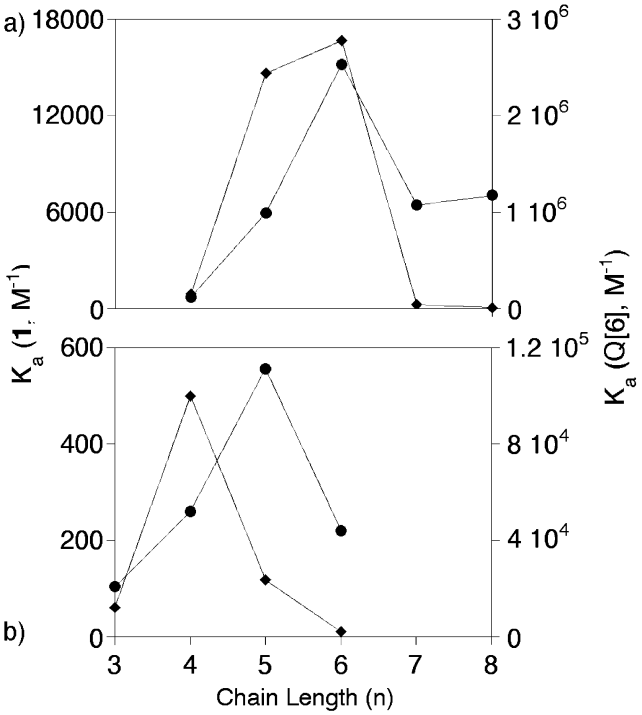


FIGURE 8. Plots of K_a versus chain length for the binding of: (a) $^+H_3N(CH_2)_nNH_3^+$ and (b) $H(CH_2)_nNH_3^+$ to **1** (●) and CB[6] (◆).

(50) Remainder of the protons on **1** are oriented toward its convex face and are not expected to show NOEs with protons on **4**.

greater flexibility of **1** is also reflected in its diminished affinity toward ammonium ions relative to CB[6]. For example, the CB[6] binds ≈ 180-fold more tightly toward its most tightly bound ammonium (**10**) and diammonium (**4**) species than **1**. The 180-fold reduction in affinity between cyclic CB[6] and acyclic **1**, while substantial, is significantly less than has been observed in related acyclic hosts (e.g. crown ethers versus podands) where preorganization is important.[23−27] This relatively small difference in affinity demonstrates that the *o*-xylylene bridges between the glycoluril rings efficiently biases **1** into the (a,a,a,a)-**1** conformation required for binding.

b. Effect of N-Methylation. Table 1 (entries 3, 10, and 11) demonstrate the influence of N-methylation on binding affinity toward **1** and CB[6]. The binding modes shown in Figures 1 and 7b depict the formation of only two hydrogen bonds; accordingly, the affinity of secondary diammonium ion **13** (Table 1, entry 10) toward **1** and CB-[6] is similar to that of primary diammonium ion **4** (entry 3). In contrast, tertiary diammonium ion **14** (Table 1, entry 11) binds only 3-fold less tightly than **4** to **1** but 189-fold less tightly to CB[6]. This difference reflects the reduced importance of formation of H-bonds in the recognition behavior of **1** compared to CB[6] and its greater flexibility.[51]

c. Effect of Branching and Width. We investigated the influence of the alkyl branching and guest width on binding within **1**. Since the cavity of **1** is shaped by only two glycoluril and three aromatic rings, it is slightly narrower than that of CB[6]. Accordingly, ammonium ions containing furyl (**15**) and aryl (**16**) rings bind relatively poorly to **1** when compared to their straight-chain analogues (ex: Table 1, entry 12 versus 8, and entry 13 versus 3). In contrast, branched alkylamines **17** and **18** bind with similar affinity to **1** as their linear counterpart, a trend also seen for CB[6] (Table 1, entry 14 versus 7, and entry 15 versus 8).

d. Effect of Functional Groups. We also investigated the influence of several functional groups (disulfide, alcohols, acids, pyridinium, and guanidinium) on the relative affinity. For example, the disulfide based complex (**1·19**) is 19-fold weaker than the **1·4** complex (Table 1, entries 16 and 3). Such differences were seen previously in CB[6] thioether complexes and attributed to the greater hydrophobicity of the methylene group.[4b] Even though diols and diacids are known[52] to bind weakly to CB[6] we were unable to detect related complexes of **1** (Table 1, entries 17 and 18). The lack of binding of **20** and **21** within **1** highlights the importance of ion−dipole interactions in the formation of complexes between **1** and ammonium ions. Accordingly, the guanidinium complex **1·22** is as strong as the corresponding ammonium complex **1·4** (Table 1, entries 19 and 3). Last, the affinity of **1** for methyl viologen is surprisingly large (−4.5 kcal/mol) given the relatively small size of the cavity of (a,a,a,a)-**1**, suggesting that the binding mode of the **1·23** complex may differ from that suggested above (Figure 7).

III. Conclusions

Cucurbituril (CB[6])[9,53] and its homologues (CB[5], CB-[7], and CB[8]) have found widespread application in both molecular recognition and self-assembly studies. The prominence of CB[*n*] in these fields is particularly notable given the fact that the tailor-made preparation of cucurbit[*n*]uril derivatives and analogues, despite significant synthetic and mechanistic work, remains an unsolved problem.[3,14−19,21,22,54−56] In this paper, we explored an approach that circumvents the synthetic challenges posed by the synthesis of macrocyclic CB[*n*] based on acyclic CB[6] congener **1**.

Acyclic CB[*n*] congeners have the potential for broad utility in supramolecular chemistry, provided that their recognition properties and binding affinities are similar to those of CB[*n*]. We achieve this similarity in practice through the use of the *o*-xylylene linking groups, which simultaneously preorganize **1** into the (a,a,a,a)-**1** conformation required for binding and minimize unwanted self-association. We find that the recognition behavior of **1** parallels that of CB[6]. For example, compound **1** binds to a wide variety of alkaneammonium and alkanediammonium ions in water ($K_a \leq 1.52 \times 10^4$ M^{-1}), exhibits length-dependent selectivity, and is competitively bound by alkali metal cations in the phosphate buffer. The binding affinity of **1** is only 180-fold lower than that of CB[6]. This reduction in affinity of acyclic **1** versus cyclic CB[6] is significantly smaller than has been observed in other systems and highlights the conformational bias imposed by the *o*-xylylene rings. These results suggest that macrocycle formation is not necessary to preserve much of the binding affinity and selectivity of CB[6] and that acyclic CB[6] congeners may extend the range of applications of CB[6].

In contrast to the current state-of-the-art in CB[*n*] synthesis, the synthesis of **1** is modular and amenable to substituents on both the terminal and central aromatic rings and on the convex face of the glycoluril skeleton. Furthermore, the CO_2Et functional groups on the convex face of the glycoluril rings provide excellent solubility characteristics and handles for subsequent derivatization and allow straightforward chromatographic purification. The use of longer terminal and central aromatic rings would result in acyclic CB[*n*] congeners with larger cavity volumes that may function as CB[7] and CB[8] surrogates. Furthermore, the opportunity to tune the recognition behavior of this class of molecules by appending functional groups to the edges of the aromatic rings suggests that acyclic CB[*n*] congeners hold promise that complements that of macrocyclic CB[*n*].

IV. Experimental Section

A. Compounds 3C and 3S. Compound **2**[22b] (0.90 g, 2.0 mmol) was dissolved in anhydrous DMSO (10 mL) under N_2,

(51) Compound **1** behaves as a CB[6] congener in that it binds tightly to alkanediammonium ions in water and exhibits length-dependent selectivity and and competitive binding with alkali metals present in solution. Compared to CB[6], the glycoluril rings of **1** play a relatively minor role in the binding process. Consider, for example, the 3.5-fold difference in affinity observed for **1·4** versus **1·14** compared to the 305-fold difference in affinity observed for CB[6]·**4** versus CB[6]·**14** (Table 1, entries 3 and 11).]

(52) Buschmann, H.-J.; Jansen, K.; Schollmeyer, E. *Acta Chim. Slov.* **1999**, *46*, 405−411.

(53) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24.

(54) Day, A. I.; Blanch, R. J.; Coe, A.; Arnold, A. P. *J. Incl. Phenom. Macrocycl. Chem.* **2002**, *43*, 247−250.

(55) Blanch, R. J.; Sleeman, A. J.; White, T. J.; Arnold, A. P.; Day, A. I. *Nano Lett.* **2002**, *2*, 147−149.

(56) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, ASAP.

and *t*-BuOK (0.60 g, 5.0 mmol) was added. After the mixture was stirred for 15 min, 1,2,4,5-tetrakis(bromomethyl)benzene (0.45 g, 1.00 mmol) was added in one portion and stirring was continued for 3 h. The reaction mixture was poured into 0.1 N HCl (1 L) and extracted with EtOAc (3 × 400 mL). The extracts were washed with brine (2 × 300 mL) and dried over anhydrous $MgSO_4$. After filtration and rotary evaporation, the residue was purified by flash chromatography (SiO_2, $CHCl_3$/CH_3CN, 3:1) to give compound **3C** (0.130 g, 0.127 mmol, 13%) and compound **3S** (0.030 g, 0.029 mmol, 3%). **Compound 3C.** Mp >350 °C (dec). TLC ($CHCl_3$/MeOH, 25:1) R_f 0.32. IR (KBr, cm^{-1}): 2979w, 2926w, 2838w, 1725s, 1461s, 1420s, 1260s, 1146m, 1081s, 1019m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (s, 2H), 6.68 (s, 4H), 5.29 (d, J = 15.8, 4H), 4.59 (d, J = 15.3, 4H), 4.31 (d, J = 15.3, 4H), 4.11 (d, J = 15.8, 4H), 4.10 (q, J = 7.1, 4H), 4.00 (q, J = 7.1, 4H), 3.75 (s, 12H), 1.20 (t, J = 7.1, 6H), 1.14 (t, J = 7.1, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 165.9, 156.3, 151.2, 135.6, 131.4, 126.5, 112.5, 80.6, 79.8, 63.2, 63.1, 57.0, 45.4, 37.2, 13.9, 13.8. MS (FAB, Magic Bullet): *m*/*z* 1023 (44, $[M + H]^+$), 750 (100). HR-MS (FAB, Magic Bullet): *m*/*z* 1023.3804 ($[M + H]^+$, $C_{50}H_{55}N_8O_{16}$, calcd 1023.3736). X-ray crystal structure, crystallized from toluene/$CHCl_3$. **Compound 3S.** Mp > 350 °C (dec). TLC ($CHCl_3$/MeOH, 25:1) R_f 0.35. IR (KBr, cm^{-1}): 2977w, 2935w, 2906w, 2834w, 1722s, 1460s, 1422s, 1256s, 1080m, 1018m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 2H), 6.68 (s, 4H), 5.29 (d, J = 15.9, 4H), 4.68 (d, J = 16.2, 4H), 4.28 (d, J = 15.9, 4H), 4.26 (q, J = 7.1, 4H), 4.16 (q, J = 7.1, 4H), 4.14 (d, J = 16.2, 4H), 3.75 (s, 12H), 1.29 (t, J = 7.1, 6H), 1.25 (t, J = 7.1, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 165.3, 155.0, 150.4, 136.6, 130.5, 126.9, 112.0, 79.9, 79.8, 63.4, 63.3, 56.5, 44.1, 36.2, 13.7, 13.7. MS (FAB, Glycerol): *m*/*z* 1023 (6, $[M + H]^+$), 103 (100). HR-MS (FAB, glycerol): *m*/*z* 1023.3755 ($[M + H]^+$, $C_{50}H_{55}N_8O_{16}$, calcd 1023.3736). X-ray crystal structure, crystallized from CH_2Cl_2. Anal. Calcd for $C_{50}H_{54}N_8O_{16}$ (1023.02): C, 58.70; H, 5.32. Found: C, 58.40; H, 5.27.

B. Compound 1. A mixture of compound **3C** (0.086 g, 0.084 mmol), LiOH (0.035 g, 1.46 mmol), deionized H_2O (35 mL), and MeOH (35 mL) was heated at 70 °C for 120 h. Excess H_2O/MeOH was removed by rotary evaporation, and the residue was dried under high vacuum. The residue was combined with PTSA·H_2O (0.302 g, 1.59 mmol) in H_2O (10 mL) and then dried under high vacuum. The resulting solid was washed with MeOH (3 × 7 mL), dried under high vacuum, redissolved in H_2O, and finally lyophilized to give **1** (0.061 g, 0.067 mmol, 80%) as a white solid. Mp > 295 °C (dec). TLC ($CHCl_3$/MeOH/HCOOH, 10:10:1) R_f 0.16. IR (KBr, cm^{-1}): 3430s, 2980w, 2930w, 2836w, 1715s, 1484s, 1384s, 1258s, 1080m. ^{1}H NMR (400 MHz, D_2O): δ 7.01 (s, 2H), 6.66 (s, 4H), 5.09 (d, J = 16.2, 4H), 4.40 (d, J = 16.2, 4H), 4.21 (d, J = 16.2, 4H), 3.90 (d, J = 16.2, 4H), 3.56 (s, 12H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.7, 166.3, 156.4, 150.7, 135.1, 131.9, 126.6, 112.4, 80.3, 80.0, 56.7, 44.3, 36.3. MS (FAB, Magic Bullet): *m*/*z* 911 (6, $[M + H]^+$), 302 (100). HR-MS (FAB, Magic Bullet): *m*/*z* 911.2470 ($[M + H]^+$, $C_{42}H_{39}N_8O_{16}$, calcd 911.2484).

C. AM1 Calculations. All computations were performed on a personal computer running PC Spartan Pro. The overall structure was created with Spartan's graphical user interface and then minimized by MMFF94 or SYBYL molecular mechanics calculations. These minimized structures served as the input files for the AM1 calculations.

D. NMR Experiments. For the ^{1}H NMR titrations and self-association experiments, the temperature was maintained at 298 ± 0.5 K with a temperature control module that had been calibrated using the separation of the resonances of methanol. A series of spectra were collected at different host concentrations (100 μM < [**1**] < 10 mM) for self-association or at constant host concentration ([**1**] = 100 μM) and guest concentrations ranging up to 50 mM for 1:1 binding. The NMR samples were adjusted to pD 7.4 after preparation when necessary. The tabulated values of chemical shift versus concentration were fitted using self-association and 1:1 binding models implemented within Scientist (MicroMath Scientific Software, Salt Lake City, Utah). Selective one-dimensional ROESY spectra were acquired using standard pulse sequences. All spectra were referenced relative to external sodium 3-trimethylsilylpropionate-d_4.

E. X-ray Crystal Structures for 3S and 3C. Detailed descriptions of the data collection and solution and refinement of the structures can be found in Supporting Information. Crystal data for **3C**: $[C_{57.56}H_{63}Cl_{10.67}N_8O_{16.22}]$ (1150.02); rhombohedral, space group *R*-3; colorless rod, a = 47.427(5) Å, b = 47.427(5) Å, c = 12.6667(18) Å; V = 24674(5) Å^3; Z = 18; T = 153(2) K; $R(F)$ = 0.0529; GOF on F^2 = 1.144. Crystal data for **3S**: $[C_{26}H_{29}Cl_2N_4O_8]$ (596.43); triclinic, space group *P*-1; colorless block, a = 10.5291(7) Å, b = 10.7853(8) Å, c = 12.3102(8) Å; V = 1390.78(17) Å^3; Z = 2; T = 193(2) K; $R(F)$ = 0.0444; GOF on F^2 = 1.107.

Acknowledgment. This work was supported by the National Institutes of Health (GM61854) and the University of Maryland. L.I. is a Cottrell Scholar of Research Corporation.

Supporting Information Available: Crystallographic data for **3C** and **3S**, packing diagrams of **3C** and **3S** in the crystal (Figures S1 and S2), the self-association and 1:1 models used by Scientist, and ^{1}H and ^{13}C spectra recorded for **3C** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034399W