JOC The Journal of Organic Chemistry

Article

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Locating the Cyclopentano Cousins of the Cucurbit[*n*]uril Family

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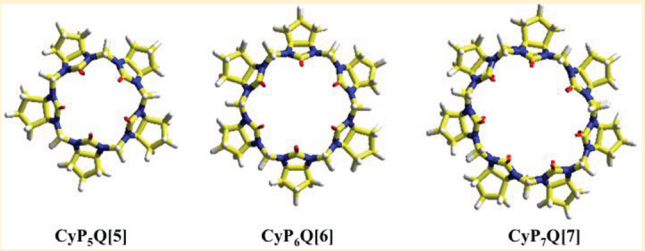
Supporting Information

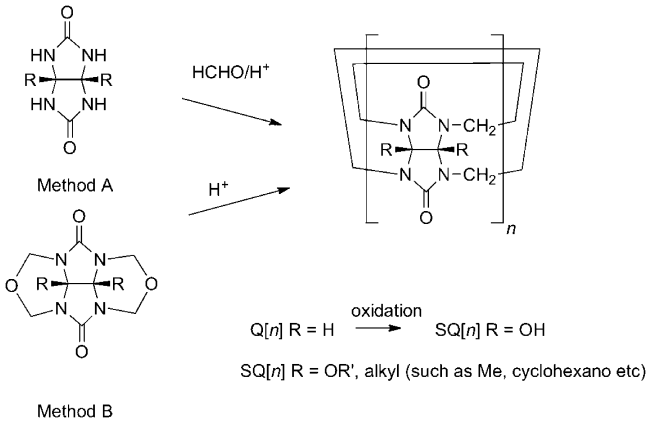
ABSTRACT: The synthesis of the first family of fully substituted cucurbit[*n*]uril is discussed, and the structural features of precursor glycolurils are highlighted in their importance to achieving higher homologues. The members of the family, where n = 5−7, have been fully characterized, and increased binding affinities have been identified for dioxane in $CyP_6Q[6]$ and adamantyl NH_3^+ in $CyP_7Q[7]$. A higher homologue is indicated but not conclusively identified.



INTRODUCTION

The synthesis of a complete set of homologues of fully substituted cucurbit[*n*]uril, SQ[*n*] has been elusive since the first report of a fully substituted Q[5] in 1992 (SQ[5], R = Me, $Me_{10}Q[5]$ Scheme 1).[1] At this time, there have been few examples of fully substituted Q[*n*] being synthesized.[2−4] Substitution on a Q[*n*] at this point in their development is defined as where the methine carbon of the glycoluril moiety bears a group, which is either an alkyl radical or an oxy radical (see SQ[*n*] of Scheme 1.).[1−4] These substituent groups are located at the equator or girth of a Q. In principle, SQ[*n*] homologues can be synthesized through the condensation of any suitably substituted glycoluril bearing a group(s) at either or both carbons bearing R of the fuse junction of the two imadazolone rings (Scheme 1). This approach has met with limited success as the predominant homologues are SQ[5]'s with only small amounts of SQ[6]'s. The alternative method for the introduction of substitution is through direct oxidation of the regular Q[*n*] to introduce an oxy radical. This too is limited, in that only Q[5] and Q[6] are amenable to the oxidative conditions. Only very low yields for the higher homologues are reported.[4]

Scheme 1. Methods A and B Are Two Possible Direct Routes to the Synthesis of SQ[*n*] from a Substituted Glycoluril or the Diether Derivative



To introduce substitution to the higher homologues remains a challenge to the area of cucurbituril chemistry. The potential gains to producing substituted Q[*n*] are (1) to modify their solubility to a range of solvents as well as to increase aqueous solubility, (2) to modify and manipulate the electronic character of both the portal and the cavity,[5−7] and (3) to provide a route to more complex structures.

We have been intrigued by the synthetic phenomenon of smaller homologue predominance with substitution. In the two reported examples of SQ[*n*] carrying full substitution either as methyl groups or as cyclohexane rings the predominance of $Me_{10}Q[5]$ is strikingly high with only 2% of $Me_{12}Q[6]$ ever being isolated.[2] The cyclohexanoQ[6] has been reported as 10% and the cyclohexanoQ[5] at 80%.[3] Some clue to SQ[5] predominance when substituted can be drawn from the cavity shape of partially substituted Q[6]'s where the substitution occurs on the α and δ glycoluril moieties as either methyl groups or cyclohexane rings.[8] These cavities are ellipsoid with the sharpest curve of the ellipse occurring at the substitution points of the Q[6]'s, i.e., the α and δ positions. This suggests that the substitution imposes a subtle angle influence upon the methylene linking groups to the next glycoluril and that if the next glycoluril is also substituted that this will result in a sharper curve as the endo-oligomer forms leading more readily to the smaller homologues.[9,10] The question arose as to whether there was a substituent group that would not impose sharper curves in the endo-oligomer. The small percentage increase in the

Received: October 25, 2011
Published: November 28, 2011

   dx.doi.org/10.1021/jo2021778 | J. Org. Chem. 2012, 77, 606−611

proportion of cyclohexanoQ[6] compared to Me_{12}Q[6] led us to contemplate the possibility that a tighter ring substituent such as a cyclopentane might improve the outcome. It was expected that the smaller 5-membered alkyl ring would subtly change the bond angles in the glycoluril structure to allow the formation of higher homologues. The support for this premise was also found in the N−C−N bond angles (β) of the concave face of the substituted glycoluril diethers **1**−**3** (Figure 1).

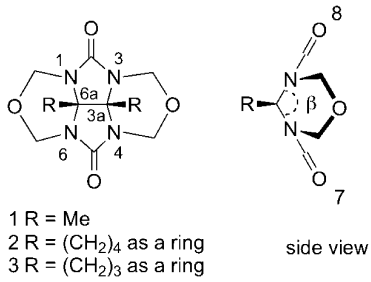


Figure 1. Substituted glycoluril diethers showing two perpendicular views highlighting atom labels and the dihedral angle β of the concave face.

We examined the crystal structures of precursor glycoluril diethers **1**−**3** and from this data formed the opinion that the synthesis of SQ[n] favorable to higher homologues should be achievable with the correct choice of substitution.

RESULTS AND DISCUSSION

Glycoluril Diethers and Structural Analysis Relative to Changes in Substitution of R. The substituted glycoluril diethers **1**−**3** were preferred for structural analysis in preference to their parent glycolurils for three reasons: (1) they can be primary intermediates to the synthesis of Q[n] (Scheme 1), (2) they incorporate the essential N alkyl group inherent in the Q structure, albeit in a 6-membered ring and not an 8-membered ring, and (3) because the potential for H-bonded structures are eliminated, this latter point is potentially a source of fluctuation in bond angles.

The single-crystal X-ray diffraction structure determinations were made for the substituted glycoluril ethers **2** and **3**, while the crystal data for **1** was sourced from the literature.[11] Examination of the data revealed a trend where the dihedral angle (β) of the concave face consistently widened with the change in substitution (R = Me **1**; cyclohexano **2**; to the smallest ring cyclopentano **3** (Table 1)).

Table 1. Selected Angles and Distances Derived from X-Ray Structures of 1−3

	glycoluril substitution R =		
	methyl[11] **1**	cyclohexano **2**	cyclopentano **3**
mean plane angle β (deg)	108.88	109.31	110.08
direct C═O distance O7−O8 (Å)	4.99	5.07	5.08

A direct comparison to an unsubstituted glycoluril as a diether equivalent of compounds **1**−**3** where R = H was not possible as this compound is unknown. However, previously in our laboratories we have analyzed the structure of the glycoluril dimer **4**, which has two β angles (Figure 2. β1 = 113.86 and β_2 = 115.16° concave face angles) and comparison to **4** indicated

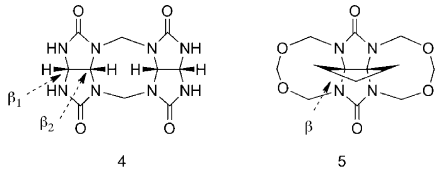


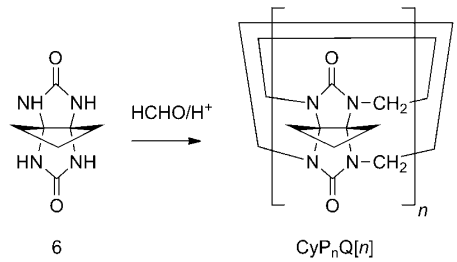
Figure 2. Indicating the two angles (β_1 = 113.86° and β_2 = 115.16°) of the concave face of the glycoluril dimer **4** and the concave face angle (β = 113.4°) of the tetraether **5**.

that the trend was in the right direction.[12] Obviously the formation of the 8-membered ring linking the glycoluril moieties also has a widening effect on the dihedral angle β_2. We have previously reported the unusual tetracyclic tetraether **5**, which has a comparable 8-membered ring with O instead of N and the concave face dihedral angle is wider (Figure 2. β = 113.4°).[13] The ultimate test to the hypothesis of the benefit to increasing the β angle was the synthesis of a substituted Q[n] where n can be equal to 7 or greater.

Synthesis of SQ[n] from Substituted Glycoluril Where R = $(CH_2)_3$ Is a Ring. The cyclopentanoglycoluril **6** was synthesized by the acid-catalyzed condensation of 1,2- cyclopentadione and urea. The highest yielding method (60%) in our hands was that reported by Gompper, where the acid catalyst was anhydrous HBF_4.[14] The use of an alternative acid catalyst such as TFA produces much lower yields.[13]

The synthesis of cyclopentanoQ[n] (Scheme 2) was evaluated under reaction conditions of acid catalysis, temper-

Scheme 2. Reaction to CyclopentanoQ[n]



ature, and reactant concentrations previously developed in our group for the synthesis of normal Q[n].[9] In addition, the influence of the templating metal ion Li^+ on the reaction outcome was assessed. This metal ion has previously been demonstrated to have a small effect toward increasing the distribution in favor of the higher homologues for normal Q[n].[15]

The condensation reaction of glycoluril **6** with paraformaldehyde was best performed in HCl 37% involving a three stage process of rt for ∼30 min; 50 °C for ∼80 min and then the temperature was increased to 90−95 °C for 3 h. Like the synthesis of normal Q[n] the mixture was always a light amber color indicating little, to no decomposition (Table 2).

Complete evaporation of the acid solvent and thorough drying gave the ^{1}H NMR spectrum of the crude reaction mixture in D_2O salt solutions with typical chemical shifts for the methylene protons resonances appropriate for an SQ[n] mixture with two multiplets at δ 4.1−4.4 and 5.4−5.7. Unlike mixtures of normal Q[n], the doublet sets for each homologue are not conveniently distinguishable. However, they can be identified by the addition of a molecular guest that is specific to a particular homologue, and by this method we were able to

dx.doi.org/10.1021/jo2021778 | J. Org. Chem. 2012, 77, 606−611

Table 2. Product Distribution of $CyP_nQ[n]$ under the Influence of a Templating Alkali Metal Ion or Reactant Concentration

		weight %[a]			
[6] mg/mL of HCl[b]	template M^+	$CyP_5Q[5]$[d]	$CyP_6Q[6]$	$CyP_7Q[7]$	$CyP_8Q[8]$
320	none	60	32	8	
320	Li^+	45	38	16	trace[f]
320	Cs^+	49	37	12	
910[c]	none	e	23	10	

[a]Weight % were determined by ^1H NMR in D_2O for the total SQ[n] mixture by comparing the relative ratios of integrals of a bound probe molecule, dioxane for SQ[6] and adamantylamine salt for SQ[7], and the SQ[n] methylene proton resonances. [b]In all experiments the HCl was 37%. [c]Reaction times were longer than normal: rt for 30 min; then 50 °C for 80 min; then 90–95 °C for 20 h. Reaction was incomplete. [d]The proportion of SQ[5] was calculated as the remaining material. [e]The proportion of SQ[5] cannot be determined due to incomplete reaction. [f]Indicated but not conclusively.

identify the presence and proportion of each homologue within a synthetic mixture (Table 2.). The probing guests used were dioxane and the salts of adamantylamine and dimethylphenanthroline.[16,17] Each of these guests, in excess, are selective for the cavities of $CyP_6Q[6]$, $CyP_7Q[7]$, and $CyP_8Q[8]$, respectively. The probing guest was added to separate samples in excess and the integrals of the bound guest resonances were compared to those of the total $CyP_nQ[n]$ methylene proton resonances and the weight ratio determined (Table 2). Corrections were made for binding ratios of 1:0.88 for dioxane, 1:1 for the adamantyl salt, and 1:2 for the salt of dimethylphenanthroline.

The $CyP_nQ[n]$ mixture was subjected to chromatography on Dowex cation exchange resin, which gave the homologues as enriched fractions. These fractions were generally two homologues with one of them enriched to ~80%. The order of elution was $CyP_6Q[6]$, $CyP_5Q[5]$, $CyP_7Q[7]$, respectively, and each of the homologues was then purified by crystallization. Purification of $CyP_6Q[6]$ was assisted by the addition of dioxane affording crystals of dioxane@$CyP_6Q[6]$, while $CyP_7Q[7]$ was purified by the addition of adamantylamine HCl and NH_4PF_6 to give crystals of (adamantylNH_3^+@$CyP_7Q[7]$)PF_6^-.

Both $CyP_5Q[5]$ and the dioxane@$CyP_6Q[6]$ have been thoroughly characterized by NMR and ESM spectroscopy as well as single-crystal X-ray diffraction. The ^1H NMR spectra were consistent with the highly symmetrical structures of $CyP_nQ[n]$ showing only four resonances as expected, the methylene proton resonances as geminally coupled doublets in the region of δ 5.6 and 4.3 and the methylene proton resonances of the cyclopentane substituent as narrow multiplets in the region of δ 2.3 and 1.7 in a ratio of 2:1, respectively (Experimental Section). These structures were further supported by ESMS giving major ions at m/z 1069 consistent with $[CyP_5Q[5] + K^+]$ and m/z 641.3 and 685.3 consistent with $([CyP_6Q[6] + 2Na]^{2+}/2)$ and $([CyP_6Q[6] + \text{dioxane} + 2Na]^{2+}/2)$, respectively.

The ^1H NMR spectrum of the dioxane@$CyP_6Q[6]$ in D_2O is also characteristic of a Q[6] cavity in that cavity-bound dioxane has slow exchange kinetics on the NMR time scale with a significant upfield shift. The shift relative to free dioxane is Δ1.03 ppm for $CyP_6Q[6]$ compared to Δ0.98 ppm for Q[6]. In addition, in the presence of an excess of dioxane (10 mol equiv) the binding ratios are 1:0.88 for $CyP_6Q[6]$/dioxane and 1:0.6 for Q[6]/dioxane. The relative binding constant of $CyP_6Q[6]$ for dioxane in competitive binding experiments between $CyP_6Q[6]$ and Q[6] was found to be K_{rel} = 1.8 ($K_{CyP6Q[6]}/K_{Q[6]}$).

X-ray Crystal Structures of $CyP_5Q[5]$·KCl and Dioxane@$CyP_6Q[6]$. The X-ray crystal structures of $CyP_5Q[5]$·KCl and dioxane@$CyP_6Q[6]$ were determined and showed the classical spheroid cavity of a Q[5] or Q[6]. In respect to the dimensions of the portal and cavity, the relative differences were the same or only differ slightly compared to the primary members of the Q family (Table 3).

Table 3. Comparison of the Dimensions[a] of $CyP_{5-6}Q[5-6]$ to Normal Q[5–6] Derived from X-ray Crystal Structures

Q[n]	portal O–O avg diam (Å)	cavity C–C avg diam (Å)	depth (Å)
$CyP_5Q[5]$ KCl	2.03	5.23	9.07
Q[5] KI[18]	2.06	5.30	9.10
dioxane@ $CyP_6Q[6]$	3.94	6.89	9.11
THF@Q[6] NaCl[19]	3.90	6.80	9.13

[a]Dimensions include the van der Waals radii.

Interestingly, the crystal packing of $CyP_5Q[5]$·KCl is similar to our recently reported structures of partially substituted SQ[5] with K^+ or Sr^{2+} and solid-state templated Q[5]·KI structures, where 6-membered beaded rings are formed (beads are SQ[5] or Q[5]) .[6–8,18] However, the difference in the case of $CyP_5Q[5]$·KCl is that there is virtually no channel formed at the core of the 6-membered ring, as the space previously available is occupied by the cyclopentane ring substituents of $CyP_5Q[5]$ (Figure S1, Supporting Information).

The dioxane association complex of $CyP_6Q[6]$ readily formed crystals suitable for X-ray diffraction. Except for the difference of an equatorial skirt of cyclopentane rings the dimensions of dioxane@$CyP_6Q[6]$ were found to be remarkably similar in their portal and cavity dimensions to the reported THF@Q[6] NaCl complex (Table 3).

Given that the dimensions of both $CyP_5Q[5]$ and $CyP_6Q[6]$ are very similar to the primary Q[5–6], in spite of the guest difference and Na^+ ion association, it is reasonable to conclude that the portal and cavity dimensions are comparable with little effect from the cyclopentane substituent.

Characterization of Homologues $n \geq 7$. 1-AdamantylNH_3^+ is a very effective molecular guest for normal Q[7] with a binding constant in the order of 10^{12}–10^{14} M^{-1} depending upon pH or the presence of salts.[16,20] In addition, protonated 2,9-dimethylphenanthroline (neocuprineH^+) is an effective guest for Q[8] for which it is also selective compared to the smaller homologues.[17] Using these two probes, we were able to determine the presence or absence of the homologues n = 7 or 8 within reaction product mixtures (Table 2).

Following chromatography, $CyP_7Q[7]$ was isolated as an association complex as (adamantylNH_3^+@$CyP_7Q[7]$)PF_6^-, which was shown to be consistent with a guest@ SQ[7]. ESMS gave the ion at m/z 1595 consistent with [adamantylNH_3^+@$CyP_7Q[7]]^+$ and the doubly charged ions 809 and 817 consistent with ([adamantylNH_3^+@$CyP_7Q[7] + Na^+]^{2+}/2$) and ([adamantylNH_3^+@$CyP_7Q[7] + K^+]^{2+}/2$) respectively. The ^1H NMR spectrum (Supporting Information) shows the $CyP_7Q[7]$ portal methylene proton resonances as a doublet at δ 5.72 and a pseudotriplet (two overlapping doublets) at δ 4.37.

dx.doi.org/10.1021/jo2021778 | J. Org. Chem. 2012, 77, 606–611

This upfield doublet pair arises from the two portals being magnetically nonequivalent due to the location of the NH_3^+ ion in only one portal. The cyclopentane ring resonances are found at δ 2.37 and 1.81 (ratio 2:1). The adamantyl proton resonances are characteristically shifted upfield to 1.36 (br s), 1.17 (d), 1.10 (br s), and 0.79 (d).[16] The magnetic nonequivalence between the two portals was also evident in the ^{13}C NMR spectrum with a small difference in the C=O (δ 156.86, 156.32) and the portal CH_2 (δ 47.14, 47.07). In total there were 11 carbon resonances recorded as would be expected, given the nonequivalence of the two portals.

The binding affinity of $CyP_7Q[7]$ for the adamantylNH_3^+ guest was found to be higher than that of Q[7]. A competitive binding experiment for adamantylNH_3^+ was conducted where Q[7] was added to adamantylNH_3^+@$CyP_7Q[7]$ in D_2O and the reaction was brought to equilibrium at 85 °C over >6 h (Scheme 3). The same experiment at rt had progressed to

Scheme 3. Competitive Binding Reaction between $CyP_7Q[7]$ and Q[7] for AdamantylNH_3^+

Q[7] + adamantylNH_3^+@$CyP_7Q[7]$ ⇌ adamantylNH_3^+@Q[7] + $CyP_7Q[7]$

<12% toward equilibrium after 45 days (Scheme 3). From the equilibration experiment, the relative binding ratio for $CyP_7Q[7]$ was determined to be $K_{CyP7Q[7]} = 1.9K_{Q[7]}$.

Predictably, the solubility of (adamantylNH_3^+@$CyP_7Q[7]$)-PF_6^- in water was reduced, which was convenient for its purification, but PF_6^- salts often have organic solvent solubility. This (adamantylNH_3^+@$CyP_7Q[7]$)PF_6^- salt was found to be soluble in CD_3CN, and the ^1H NMR spectrum was consistent with the adamantylNH_3^+ remaining cavity bound. The only significant change was that downfield methylene proton resonance which occurred as one doublet (δ 5.72) in D_2O separated into two clearly defined doublets (δ 5.71 and 5.79) in CD_3CN as the solvent.

$CyP_8Q[8]$ could not be confidently detected in product mixtures although there were resonances observed after the addition of the Q[8] selective neocuprineH$^+$ that were consistent with this guest encapsulated in a $CyP_8Q[8]$ cavity.

CONCLUSION

We report the first example of a family of fully substituted cucurbit[*n*]uril. It has been clearly demonstrated that the dihedral angle of the concave face of the starting glycoluril is important in determining whether higher homologues will form. A simply substituted glycoluril ether where R = Me, **1** (Figure 1), has the sharpest angle on the concave face compared to glycoluril ethers **2** and **3** as a consequence of steric repulsion between the two methyl groups. The steric repulsion is alleviated by the introduction of a 6-membered ring as in **2**, and the concave face angle is widened. Introducing a 5-membered ring as in **3** further widens the angle. The consequence is that the natural curvature of the growing precursor oligomers[9,10] formed in the acid-catalyzed synthesis of cucurbit[*n*]uril (Scheme 2) is larger, and therefore, the potential for higher homologues is higher. This can also be manipulated to a small degree by the addition of templating alkali metal ions to the reaction. The cavities of cucurbit[*n*]uril where $n \geq 6$ are of prime interest as these homologues offer the greater opportunities for molecular host–guest chemistry. The new cyclopentanoQ[*n*] developed in this study suggest opportunities related to increased binding constants as demonstrated for the neutral guest dioxane and the ionic guest adamantyl ammonium ion.

We are currently engaged in further research to develop and exploit these opportunities.

EXPERIMENTAL SECTION

General Procedures. The starting materials were purchased from commercial sources and were used without purification. NMR spectra were recorded at 400 MHz for the ^1H nuclei and 100 MHz for the ^{13}C nuclei. Chemical shifts for ^1H are reported with the solvent as the internal standard D_2O 4.83 ppm and ^{13}C with external dioxane 67.4 ppm. All NMR experiments were conducted at 25 °C unless otherwise stated.

Synthesis of Tetracyclic Diethers 1–3. The tetracyclic diether **2** was prepared according to the previously reported method.[21] **1,6:3,4-Bis(2-oxapropylene)tetrahydro-3a,6a-propanoimidazo[4,5-*d*]imidazol-2,5(1*H*,3*H*)-dione (3).** A solution of paraformaldehyde (1.5 g, 50 mmol) was prepared in a vigorously stirred mixture of water (3.6 mL) and 37% HCl (2.9 mL) which was heated to 50 °C. When the paraformaldehyde had completely dissolved the solution was cooled to rt. Cyclopentanoglycoluril **6**[13,14] (0.91 g, 5 mmol) was then added in one portion to the cooled mixture and stirred at rt for 18 h. The heavy white precipitate was collected by filtration, washed with ethanol, and air-dried giving a mixture (1.39 g) of the required product **3** and 1,6:3,4-bis(2,4-dioxapentylene)tetrahydro-3a,6a-propanoimidazo[4,5-*d*]imidazol-2,5(1*H*,3*H*)-dione (tetracyclic tetraether) **5**.[13] The ratio of **3** to the tetracyclic tetraether was ~1:19 by ^1H NMR. Slow vapor diffusion of acetone into a formic acid and acetic acid solution of the product mixture gave colorless crystals of **3** (0.04 g, 3%). Alternatively, the tetracyclic tetraether (1.27 g) was heated in a mixture of formic and acetic acids at 100 °C followed by slow cooling to rt over 1 day gave **3** in a higher yield (0.48 g, 46%). Mp: > 260 °C. IR (KBr, cm^{-1}): 3441w, 2986w, 2936 m, 1728s, 1748s, 1466s, 1412s, 1381s, 1323s, 1254s, 1018s, 937s, 895s, 768s, 575 m, 424 m. ^1H NMR (400 MHz, DMSO-d_6): δ 5.22 (d, J = 11.6 Hz, 4H), 4.89 (d, J = 11.2 Hz, 4H), 2.23 (t, J = 6.8 Hz, 6H), 1.87–1.80 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 80.1, 71.1, 35.0, 24.5. MS (ESI): m/z 289.3 (100, $[M + Na]^+$). Anal. Calcd. For $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.48; H, 5.11; N, 20.78.

Typical Reaction Conditions for the Synthesis of Cyclopentanocucurbit[*n*]uril. HCl (37%, 4 mL) was added to a mixture of cyclopentanoglycoluril **5** (1.28 g, 7 mmol), paraformaldehyde (0.448 g, 14.9 mmol), and Li_2CO_3 (80 mg, 1.1 mmol). After being stirred at rt for 30 min, the mixture was heated at 50 °C for 80 min and then was heated at 90–95 °C for 3 h. The resultant light amber solution was cooled to rt, and the HCl removed in vacuo. Water (10 mL) and acetone (5 mL) were added to the residue, and the precipitate was collected by filtration, washed with acetone, and then dried to give a nearly colorless solid mixture of products (1.42 g). The crude homologues (250 mg) were dissolved in a minimum volume of formic acid (50%) and applied to a column of ion-exchange resin Dowex 50WX2. The products were eluted with 50% formic acid solution of 0.5 M HCl. The homologues eluted in the order of $CyP_6Q[6]$, $CyP_5Q[5]$, and $CyP_7Q[7]$, respectively. The solvent was removed in vacuo, and the fractions were dried for 12 h (100 °C at 0.3 mmHg). Fractions containing predominantly $CyP_6Q[6]$ (99 mg) were crystallized from water with the addition of dioxane, $CyP_5Q[5]$ (53 mg) crystallized from water, and $CyP_7Q[7]$ (23 mg) were crystallized from water after the addition of 1-adamantylNH_2·HCl and NH_4PF_6.

Cyclopentanocucurbit[5]uril ($CyP_5Q[5]$). Mp > 260 °C. IR (KBr, cm^{-1}): 3412s, 3385s, 1734s, 1471s, 1461s, 1382m, 1333m, 1294w, 1170w, 933m, 908m, 766w. ^1H NMR (400 MHz, D_2O): δ 5.62 (10 H, d, J = 16 Hz), 4.38 (10 H, br), 2.26 (20 H, narrow m), 1.75 (10 H, narrow m); (alternative 0.1 M KCl D_2O) δ 5.67 (10 H, d, J = 16 Hz), 4.45 (10 H, d, J = 16 Hz), 2.34 (20 H, narrow m), 1.85 (10 H, narrow m). ^{13}C NMR (100 MHz, D_2O): δ 156.2, 84.8, 46.5, 37.0, 23.5. MS (ESI): m/z 1069.4 (100, $[M + K]^+$). Anal. Calcd for $C_{45}H_{50}N_{20}O_{10}·8H_2O$ (1175.14) C, 45.99; H, 5.66; N, 23.84. Found: C, 45.59; H, 5.64; N, 24.02. **Dioxanecyclopentanocucurbit[6]uril**

dx.doi.org/10.1021/jo2021778 | J. Org. Chem. 2012, 77, 606–611

(**Dioxane@CyP$_6$Q[6]**). Mp > 260 °C. IR (KBr, cm^{-1}): 3468 m, 3412 m, 1750s, 1734s, 1469 m, 1461 m, 1325 m, 1292w, 929 m, 908w. ^{1}H NMR (400 MHz, D$_2$O): δ 5.66 (12 H, d, J = 16 Hz), 4.32 (12 H, d, J = 16 Hz), 2.67 (8H, s, dioxane@ CyP$_6$Q[6]), 2.30 (24 H, narrow m), 1.75 (12 H, narrow m). ^{13}C NMR (100 MHz, D$_2$O): δ 156.6, 85.2, 67.2 (dioxane@ CyP$_6$Q[6]), 46.8, 35.0, 23.6. MS (ESI): m/z 641 (100, [M + 2Na]$^{2+}$/2) 685 (95, [M + dioxane + 2Na]$^{2+}$/2). Anal. Calcd for $C_{54}H_{60}N_{24}O_{12}\cdot C_4H_8O_2\cdot 16H_2O$ (1175.14) C, 43.17; H, 6.25; N, 20.83. Found: C, 43.20; H, 6.23; N, 20.65. **1-Adamantylammonium@cyclopentanocucurbit[7]uril Hexafluorophosphate (1-AdamantylNH$_3^+$@CyP$_7$Q[7])**. Mp > 260 °C. IR (KBr, cm^{-1}): 3462s, 3408s, 1734s, 1718s, 1456 m, 1448 m, 1323 m, 1313 m, 1292 m, 1163w, 932 m, 910w, 849 m. ^{1}H NMR (400 MHz, D$_2$O): δ 5.72 (14 H, d, J = 15.6 Hz), 4.37 (14 H, t, J = 15.6 Hz), 2.37 (28 H, narrow m), 1.81 (14 H, narrow m); [1.36 (H, s), 1.17 (H, d, J = 13.2 Hz), 1.10 (H, s), 0.79 (H, d, J = 10.4 Hz) adamantyl resonances]. ^{13}C NMR (100 MHz, D$_2$O): δ 156.9, 156.3, 85.5, 52.8, 47.14, 47.07, 41.0, 35.0, 34.2, 29.1, 23.4. MS (ESI): m/z 809 (70, [M + (1-adamantylNH$_3^+$) + Na$^+$]$^{2+}$/2, 817 (100, [M + (1-adamantylNH$_3^+$) + K$^+$]$^{2+}$/2. HRMS for $C_{73}H_{88}N_{29}O_{14}$ [M + (1-adamantylNH$_3^+$)]$^+$: calcd 1594.7066, found 1594.7072.

Modification of the Reaction Conditions for the Synthesis of Cyclopentanocucurbit[*n*]uril. Alternative reaction conditions which relate to Table 2 were the same as the typical procedure above except that CsCl (2.2 mmol) replaced Li_2CO_3 or no metal salts were used.

The reaction at high reactant concentration was performed by adding 37% HCl (0.1 mL) to a mixture of cyclopentanoglycoluril **5** (91 mg, 0.5 mmol) and paraformaldehyde (31.5 mg, 1.05 mmol) at rt with stirring for 30 min. The mixture was then heated to 50 °C for 80 min and then 95 °C for 20 h. The workup procedure was the same as that described above for the typical synthesis. ^{1}H NMR analysis showed the proportion of each homologue (Table 2) plus oligomer (~40%) indicating incomplete reaction.

Comparative Binding Studies. Comparative binding studies were performed in D$_2$O at the specified temperatures and pD conditions. Comparative binding studies for CyP$_6$Q[6] (0.25 mM) relative to Q[6] and limited guest dioxane (relative initial ratio1:2.3:0.5) were performed in 10 mM buffer of K-($C_6H_4CO_2DCO_2$)/DCl pD 4.0.

The comparative binding of CyP$_7$Q[7] and Q[7] was performed by adding a Q[7] solution to (adamantyl NH$_3^+$@CyP$_7$Q[7])PF$_6^-$ 0.25 mM to a ratio of 1:1 (no buffer solution pD 3.5). Equilibrium was then forced to conclusion at 85 °C over 12 h.

X-ray Crystallographic Analyses. The crystal data for each compound was collected on a diffractometer using graphite-monochromated Mo KR radiation (λ) 0.71073 Å) with ω scan mode. Structural solution and full matrix least-squares refinement based on $F2$ were performed with the SHELXS-97 and SHELXL-97 program package, respectively. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were generated geometrically. Crystals of the tetracyclic diethers **2** and **3** were prepared by the slow diffusion of acetone vapor into aqueous solutions of these glycoluril derivatives. Crystals of the tetracyclic tetraether **5** were prepared by the slow diffusion of acetone into a DMSO solution of **5**. Crystal data for **2** (CCDC-848923): [$C_{12}H_{16}N_4O_4$] (280); monoclinic, space group $P2(1)/n$; colorless block, a = 8.402(3) Å, b = 11.908(4) Å, c = 12.710(4) Å; α = 90.00°, β = 101.856(13)°, γ = 90.00°,V = 1244.5(7) Å^3; Z = 4; T = 273(2); $R(F)$ = 0.0392; GOF ON F^2 = 1.051. Crystal data for **3** (CCDC-670588): [$C_{11}H_{14}N_4O_4$] (268); orthorhombic, space group $Pnma$; colorless block, a = 12.4218(7) Å, b = 11.3954(7) Å, c = 8.1359(5) Å; α = 90.00°, β = 90.00°, γ = 90.00°, V = 1151.65(12) Å^3; Z = 4; T = 293(2); $R(F)$ = 0.0374; GOF ON F^2 =1.058. Crystal data for **5** (CCDC-670589): [$C_{13}H_{18}N_4O_6$] (326); orthorhombic, space group $Pnn2$; colorless block, a = 10.0897(8) Å, b = 10.5987(9) Å, c = 6.5148(5) Å; α = 90.00°, β = 90.00°, γ = 90.00°,V = 696.68(10) Å^3; Z = 2; T = 293(2); $R(F)$ = 0.0405; GOF ON F^2 =1.130.

Single crystals of CyP$_5$Q[5] and CyP$_6$Q[6] were prepared from aqueous solutions of KCl or water solutions with the slow infusion of dioxane. Many of the water molecules in the crystal lattice have not been rigorously defined, but the cucurbituril complexes are well-defined. Crystal data for **CyP$_5$Q[5]2KCl·19H$_2$O** (CCDC-748653): [$C_{135}H_{258}Cl_6N_{60}O_{87}K_6$]; monoclinic, space group $P21/c$; colorless block, a = 20.2298(8) Å, b = 33.2253(11) Å, c = 29.4252(10) Å; α = 90.00°, β = 95.186°(2), γ = 90.00°,V = 19696.9(12) Å^3; Z = 4; T = 273(2); $R(F)$ = 0.0405; GOF ON F^2 =1.052.

Crystal data for **dioxane@CyP$_6$Q[6]·18.5H$_2$O** (CCDC-848924): [$C_{116}H_{208}N_{48}O_{61}$]; monoclinic, space group P 21/c; colorless block, a = 12.6912(5) Å, b = 12.5739(5) Å, c = 23.0762(10) Å; α = 90.00°, β = 98.670°(2), γ = 90.00°,V = 3640.4(3) Å^3; Z = 1; T = 293(2); $R(F)$ = 0.0405; GOF ON F^2 =1.090.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

■ ASSOCIATED CONTENT

Supporting Information

Some crystal structure images are available excluding water molecules of CyP$_5$Q[5]KCl, dioxane@ CyP$_6$Q[6], compounds **2**, **3**, and **5** showing the dihedral angle of the concave face, and ^{1}H and ^{13}C NMR spectra of purified **3**, CyP$_5$Q[5]KCl, dioxane@ CyP$_6$Q[6], and adamantylNH$_3^+$@CyP$_7$Q[7] PF$_6^-$. X-ray data (CIF) for the structures reported herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

This work was supported by the Australian Defence Force Academy for the UNSW Early Career Researcher Grants.

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