Controlling Factors in the Synthesis of Cucurbituril and Its Homologues

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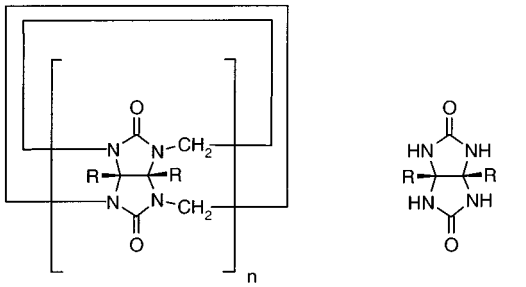
The acid-catalyzed synthesis of cucurbit[*n*]urils from formaldehyde and glycoluril is poorly understood. In this paper, we examine a wide range of reaction conditions that include the effects of acid type, acid concentration, reactant concentrations, and temperature to both probe the mechanism and optimize the yields of isolated cucurbit[*n*]urils, where $n = 5-10$. A mechanism for the formation of these cucurbit[*n*]urils is presented. Individual cucurbit[*n*]urils were unambiguously identified in reaction mixtures using ESMS and ^{13}C NMR.

Cucurbituril **1** is a remarkably robust macrocyclic host molecule that has a rigid cavity capable of binding small guests under a variety of conditions.[1−12] It is synthesized from glycoluril **2** (R = H) and formaldehyde under acidic conditions. Cucurbituril was first synthesized in 1905 by Behrend et al.[13] as an acid-soluble, crystalline product that they were unable to fully characterize. It was not until 1981, when Freeman, Mock, and Shih[14] reexamined this product that the highly ordered and symmetrical structure of cucurbituril was found to be six glycoluril units linked by pairs of methylene bridges derived from formaldehyde. The structure of **1** resembles a flattened sphere, truncated top and bottom, with a hollow core. In 1992, Flinn et al.[15] synthesized a methyl-substituted cucurbituril **3** that was determined to have five, rather than six, units of dimethylglycoluril **2** (R = Me). According to the nomenclature suggested by Flinn, **3** is decamethylcucurbit[5]uril and Berhend's original compound **1** is cucurbit[6]uril. For brevity hereafter, we will abbreviate cucurbit[*n*]uril as Q*n*, so **1** is Q6 and **3** is Me_{10}Q5. Until recently, all published work that refers to cucurbituril really only describes work with **1**, Q6.



1: R = H, n = 6
3: R = Me, n = 5

2: R = H, Me, Ph

With the discovery of Q*n*,[16,17] we were puzzled by the observation that Q6 is produced in preference to any other Q*n*. The reasons for this have been unclear. Semiempirical AM1 calculations suggest that there should be no preference for a particular ring size, and the gas-phase heats of formation, per glycoluril unit, appear to be almost identical for Q4−10. The only substituted Q*n* known at present is **3** and, semiempirical AM1 calculations for Me_{2n}Q*n* are similar to the results for Q*n*. The report of **3**, rather than the hypothetical Me_{12}Q6, suggests that methyl−methyl clashes may dominate the synthetic process. However, molecular modeling does not support this explanation for Me_{2n}Q*n* smaller than Me_{16}Q8 (Supporting Information, Table S1). The effects of hydrogen-bonding interactions, selective solvation, and counterions nevertheless could be controlling factors favoring the preferential synthesis of Q6. These factors are not easily included in AM1 calculations.

The reaction conditions described for the original synthesis of **1**,[13,18] and the minor variations to synthesize

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Table 1. Observed Positive-Ion ESMS Peaks (*m*/*z*) of a CsCl Solution of Q5−8.[a,b]

n	parent ion, P	$[P + Cs]^+$ (P + 132.9)	$[P + 2Cs + Cl]^+$ (P + 300.8)	$[P + 2Cs]^{2+}$ (P + 265.8)/2
5	$C_{30}H_{30}N_{20}O_{10}$ (830)	963.0	1131.0	548.0
6	$C_{36}H_{36}N_{24}O_{12}$ (996)	1129.1	1297.0	631.0
7	$C_{42}H_{42}N_{28}O_{14}$ (1162)	1295.0	1463.0	714.0
8	$C_{48}H_{48}N_{32}O_{14}$ (1328)	1461.0	1628.9	797.2

[a] Q8 is almost insoluble in aqueous CsCl solutions, and these ions were observed only for pure material. [b] Lower cone voltages predominantly gave the double-charged ions.

Q5−8,[17] were scrutinized in order to develop an understanding of the factors acting to produce Q*n*. In reexamining the original, particularly harsh, reaction conditions, we observed substantial quantities of ammonium salts of Q6, suggesting decomposition of starting materials or products. Milder reaction conditions might allow the formation of other Q*n* or prevent their possible destruction. We examined a wide range of reaction conditions, including the effects of acid type, acid concentration, reactant concentrations, and temperature, to both probe the mechanism and optimize the yields of individual Q*n*.

Early in this study, we recognized previously undescribed trends in electrospray mass spectroscopy (ESMS) and ^{13}C NMR data that allowed us to identify known Q*n* and hitherto unknown Q9 and Q10 in reaction mixtures. Alkali metal cations have been shown to solubilize **1** by complexation with the carbonyl portals,[4,12,19,20] and we find that they also solubilize Q5−10 to varying degrees. ESMS analyses of CsCl/Q*n* solutions gave positive ions (at a cone voltage of 100 V), with a major set of peaks for each Q*n* as the associated Cs^+, $(2Cs)^{2+}$, and $(2Cs + Cl)^+$ ions (Table 1).

These sets of ions, and the propensity to form double-charged ions, aid identification of new Q*n* as pure material as well as Q*n* in mixtures. We also found that the identification of unknown Q*n* was supported by the use of an observed trend in the ^{13}C NMR resonances. The ^{13}C NMR resonances for each of the three chemically different carbons of Q*n* show a progressive downfield shift as the value of *n* increases from 5 to 8. The downfield shift is most pronounced for the methylene and methine carbons (Supporting Information, Table S3, Figure S1).

We observed a strong correlation ($R^2 > 0.99$) between the chemical shifts of the methylene and methine carbons and the number of units, *n*, in Q*n*. We predicted the chemical shifts of previously unknown Q*n* by extrapolating the curves. This alerted us to weak ^{13}C resonances, indicating potentially new Q*n*. The intensities of ^{13}C NMR resonances, rather than ^1H NMR resonances, were used to determine the product distributions (Supporting Information, Table S4). While the ^1H NMR spectra were characteristic of each of the pure Q*n*, it was not possible to use these data to determine product distributions due to peak overlap in the spectrum of mixtures.

Factors Influencing Product Distribution. A major aim of our study was to determine which factors govern the proportional distribution of each cucurbituril homologue. The previously published two-step procedures[13,17,21] of first reacting formaldehyde and glycoluril in HCl to form an oligomer[22] and then synthesizing Q*n* in H_2SO_4 are unnecessary. We find that the reaction can be carried out in one pot with any individual strong acid and can be driven to completion to form a mixture of Q*n* (Table 2). If heated to 100 °C, the reaction proceeds through a number of physical changes and is virtually complete within 2 h to give a nearly quantitative yield of Q*n*. Following the progress of the reaction by either ^1H or ^{13}C NMR helped to define the intermediate oligomers and the conditions under which they form.

Table 2. Effect of Acid Type and Reactant Concentrations on Product Distribution

[glycoluril] mg/mL acid	acid[b]	weight %[a] Q5	Q6	Q7	Q8[c]
155−190	concd H_2SO_4	12	88	<1	<1
155−190	9 M H_2SO_4	23	44	25	8
155−190	concd HCl	17	48	28	7
155−190	9 M HCl	17	50	25	8
155−190	5 M HCl	9	52	35	4
155−190	50% HBF_4	28	43	24	5
155−190	melt TsOH	5	61	27	7
0.125	concd HCl	58	42		
1700[d]	concd HCl	3	44	33	12

[a] Weight percentages were determined by ^{13}C NMR and include a correction factor (Supporting Information). [b] Reaction temperatures were at 100 °C over a 2−3 h period, and in all cases, the reaction mixtures were homogeneous throughout the process. [c] Less than 1% of products that could be attributed to Q*n* where $n > 8$ (except for 1700 mg/mL glycoluril in concentrated HCl). [d] Solid paraformaldehyde was used rather than the equally effective 40% aqueous solution of formaldehyde. Solid paraformaldehyde enabled a high concentration of glycoluril.

The ^{13}C NMR spectrum of the initial product(s) generated at room temperature showed four major broad, cone-shaped peaks at 52−55.2, 67.0−70.0, 70.05−73.0, and 157.5−158.5 ppm. After heating to 50 °C over 1−2 h was carried out, the spectrum resolves into three sharper cones. The resonances between 67 and 70.0 almost disappear. The ^1H NMR at the same early stages shows three broad, overlapping cones with no fine structure between 3.9 and 6.1 ppm. After further heating was carried out, the center broad peak almost disappears and is replaced by two relatively sharp peaks with some developing fine structure. These two peaks are similar in shape and chemical shift positions to those of a poorly resolved mixture of Q*n*, suggesting that the oligomer at this stage is simpler and perhaps linear. No Q*n* formed after 2 h at 50 °C. After prolonged heating (several days) was carried out, the broad ^{13}C NMR peaks decrease in intensity and sharp signals attributable to each of the Q*n* appear. The relative proportions of the Q*n* varied according to the acid type, concentration of reagents, and temperature of reaction.

Effect of Acid Type. Table 2 summarizes the effects of varying the acid type and reactant concentration on the final distribution of product Q*n*. More extensive data are given in Supporting Information, Table S4.

Concentrated H_2SO_4 gave only 12% of Q5 using our milder conditions, with the remainder of Q*n* being Q6 (Q7 and Q8 were undetectable). In HCl, the product distribution was shifted as the acid concentration was

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decreased, favoring the production of Q6 and Q7. The product distribution for any given set of conditions was reproducible (±3%) provided that the glycoluril was completely dissolved in HCl before the addition of formaldehyde. If the glycoluril was not dissolved, the proportion of Q5 decreased by 10% or more (related to reactant concentration effects). Below 5 M HCl, the final steps in the reaction to form Q*n* became inefficient and incomplete, and it appears that the acid concentration was insufficient to catalyze conversion of the oligomer into the Q*n*. Concentrated HCl, 9 M HCl, 9 M H_2SO_4, and ~6 M HBF_4 show similar product distributions (Table 2).

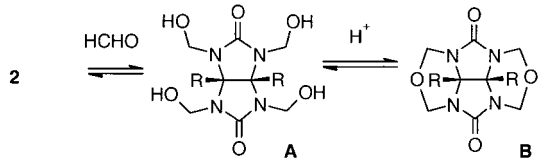
The formation of Q*n* was also achieved in a melt of *para*-toluenesulfonic acid by combining the reactants and heating the mixture to 110 °C. The product distribution markedly favored Q6 and Q7. By contrast, TFA is unable to catalyze the reaction beyond the oligomer stage and no Q*n* was formed.

Effect of Reactant Concentrations. If the length of the oligomer is the main determinant of the size of the Q*n*, then varying the reactant concentrations should change the ratio and even the range of Q*n* formed. The distribution of reaction products previously discussed was obtained with glycoluril concentrations ranging from 155 to 190 mg/mL of acid. When the glycoluril concentration was reduced to 125 μg/mL of acid, considerable decomposition of the glycoluril occurred, and the only Q*n* that were detected were Q5 and Q6 (Table 2). Increasing the concentration of glycoluril to 1.7 g/mL of acid significantly changed the Q5−8 distribution, discriminating against Q5 and producing higher Q*n*. Two new sets of characteristic Q*n* ^{13}C NMR resonances were observed—one at a higher field than Q8, the other below Q5. The chemical shifts of the high-field set agree with those predicted for Q10, but the other set did not agree with a hypothetical Q4 (Supporting Information, Figure S1). Repeated recrystallization of the reaction mixture in order to isolate Q10 gave a crystalline material that contained two sets of Q*n* resonances. ESMS established a double-charged molecular ion ($[P + 2Cs]^{2+}$, m/z = 1378) for Q15, suggesting that the structure was Q10 tightly associated with Q5. This was verified by displacing the bound Q5 with ^{13}C-labeled Q5. A feature of guests inside Q*n* is an upfield shift of the resonances in NMR spectra[23] consistent with our proposal for Q5 inside Q10, Q5@Q10. A detailed characterization and discussion of this unprecedented new product is described in a subsequent paper.[24] Interestingly, a set of ^{13}C NMR resonances for Q9 could be observed only when the high-concentration reaction was carried out with ^{13}C-enriched paraformaldehyde or in concentrated filtrates from successive recrystallizations. ^{13}C-Enrichment allows the observation of methylene resonances that fit the chemical shift trend for Q*n* up to a possible Q16, (<1%).

Nonhomogeneous reactions, where the glycoluril is not completely dissolved before the addition of formaldehyde, resemble concentrated reactions with regard to product ratios.

Effect of Reaction Temperature. In concentrated HCl, the ideal conversion temperature of the oligomer to the Q*n* was 100 °C, although conversion was possible at 50 °C with extended reaction times (greater than 4 weeks to reach completion). Under these cooler reaction conditions, the product distribution was essentially the same as that for 100 °C, except for a small set of methylene and methine resonances, consistent with those of Q9 (~1%). In the first few days, Q5 was considerably less abundant compared to the final proportion. Heating Q5, Q6, or Q7 individually in concentrated HCl for 24 h at 100 °C showed no interconversion and no detectable decomposition. By contrast, Q8 in concentrated HCl at 100 °C contracted to Q5, Q6, and Q7 (4, 13, and 38%, respectively) after 24 h, with 45% of Q8 remaining unchanged. This conversion of Q8 to smaller homologues is too slow to significantly contribute to the synthetic outcome, although it is possible that larger homologues are less thermally stable. The very low level of Q9 (<1%) suggests that under these reaction conditions, the larger Q*n*, or at least the open oligomers of a unit length of 9, are thermally unstable.

Scheme 1



At room temperature, no Q*n* were formed in concentrated HCl after 1 month; but in concentrated H_2SO_4, Q6 was almost quantitatively produced (>95%) after 2 months. We expect the dehydrating ability of concentrated H_2SO_4 to drive the equilibrium toward Q*n* products, whereas the high concentration of water in other acid systems favors the reverse reaction.

Factors Influencing the Reaction Mechanism. The primary stage of the reaction to Q*n* is an acid-catalyzed condensation of glycoluril **2** and formaldehyde, which is rapid and facile (Scheme 1).

Where R = H, type **A** intermediates are formed under basic conditions.[25] No intermediates of type **A** or **B** have been observed under acidic conditions as they react too rapidly, even at room temperature, beyond the monomer stage to form oligomers (Scheme 2). Where R = Me, the initial isolated product is of type **B** under acidic conditions.[26] In our experience, for R = Me, the tetracyclic diether **B** can be converted to Me_{10}Q5 but at much higher yields (85%) than previously reported (16%).[15] This demonstrates the reversible nature of the hydroxymethylation and subsequent ether formation, as in this case, there are 2 equiv more of the methylene linkers than are necessary to form Me_{10}Q5.

The average length of the oligomers formed from the acid-catalyzed glycoluril **2** (R = H) and formaldehyde condensation has been difficult to determine, as they are only soluble in aqueous acid solutions and formic acid. Both TOF-MALDI and ESMS have been unsuccessful. Determination of the oligomer length by end-group functionalization was also unsuccessful. ^{1}H NMR of the oligomer mixture showed <2% Q*n*, using dioxane as a probe (see Experimental Section). Despite washing the oligomer with aqueous CsCl solutions in which the Q*n*

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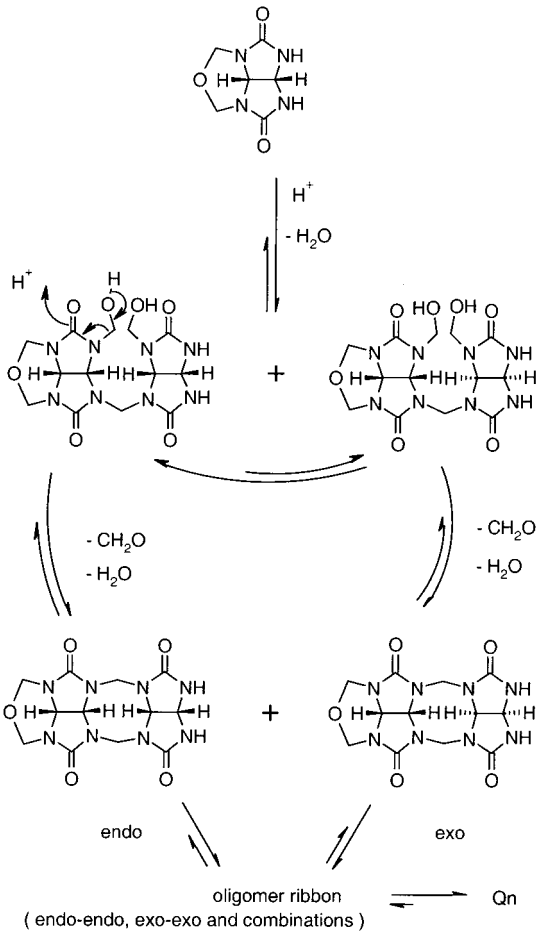
Scheme 2



are soluble and the oligomers are not, we observed only the ions for the Q*n* (as cesium complexes), albeit weakly.

A repetitive series of reactions leads to the precursor oligomers required for the formation of Q*n* (Scheme 2). We show intermediates containing ethers in our representation of the mechanism for the sake of simplicity; however, it is clear that these can be hydrated under acidic conditions to diols and tetraols of type **A** or even be absent with only terminal NH functionality. Reaction equilibrium arrows demonstrate our view that all the reactions are reversible.

A weighting (as indicated by the equilibrium arrows) has been given for these reactions, on the basis of predicted thermodynamic outcomes combined with a perceived chemical outcome.

The same types of nucleophiles and electrophiles shown in Scheme 2 are likely to occur repeatedly until stable Q*n* are formed. Not all possible combinations or intermediates leading to oligomerization are represented, but it should be inferred that many variations exist.

Interpretations. We have sought to identify why Q6 is the favored product in the synthesis of Q*n*. The answer might lie in the range of thermochemical stabilities of Q*n*, oligomer length, templating effects, or a combination of these. Although none of the individual precursor oligomers have been isolated, they are observed in the ^{13}C NMR spectra as complex mixtures. There is no reason to suspect the formation of short oligomers as they remain in solution during reaction and are not terminated by precipitation. One reason for the apparent complexity is likely to be associated with the relative

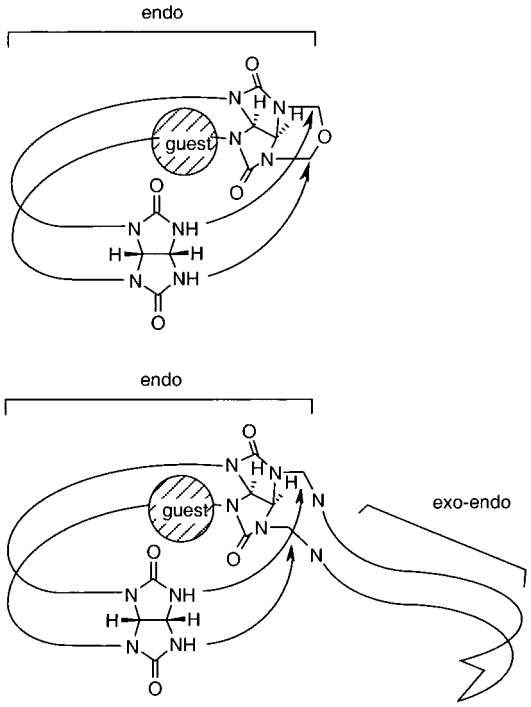


Figure 1. Formation of cyclic Q*n* from endo−exo oligomer ribbons.

orientation of the glycoluril moieties. The glycolurils are composed of two cis-fused five-membered rings, and they can orient themselves in two ways when linked by methylene bridges: with both concave faces on the same side (endo) or on opposite sides (exo). AM1 calculations suggest that the all-endo intermediates are more stable than endo−exo combinations, particularly if solvation is taken into account (Supporting Information, Table S2). As there are many combinations possible for endo−exo oligomers, the ^{13}C NMR spectrum is complex. The ^{1}H NMR spectrum shows that the methylene protons are anisotropic, as they are in all Q*n*. Kinetically, any endo−exo arrangement is initially possible but only the all-endo conformation can close to form a Q*n* (Figure 1). Any oligomer with concave faces on opposite sides (exo−endo combinations) must disconnect and reconnect for it to flip into the all-endo conformer (Scheme 2). Since Q8 can contract to smaller Q*n*, acid-catalyzed disconnection and reconnection of the methylene linkers is demonstrated as a reversible step. The oligomeric, ribbonlike structures do not have to become all-endo over their entire lengths but only over a length sufficient to allow them to close to a Q*n*. Upon closure of the oligomer, the remaining fragment is clipped off, either enabling it to condense with other oligomers or, if it is of a suitable length, rearrange and self-condense to form another Q*n*.

Q*n* might be formed by head-to-tail condensation of the oligomer, condensation at an intermediate point of an extended oligomer, or both (Figure 1). In principle, oligomers could be formed from a large number of glycoluril units and, through a process of stepwise disconnection and self-condensation, cyclize to form Q*n*. Our high-dilution experimental conditions limited the rate at which the oligomer achieved a length beyond 5 or 6 units before it condensed. As expected, smaller Q*n* were favored and Q5 was the major product. When Me_{10}Q5 is formed from tetracyclic diether **B**, no oligomers or Me_xQ*n* homologues were detected under the reported

reaction conditions. This suggests that the oligomer is built up to a unit length of 5, where it immediately condenses to form Me_{10}Q5. We are continuing to investigate the effect of reactant concentration on this system.

Q5−7 were thermally stable in concentrated HCl for at least 24 h at 100 °C. Under the same conditions, Q8 began to contract to smaller Q*n*. The rate of ring contraction of Q8 was slowed when the reaction mixture was heated in concentrated HCl in the presence of 10 mol equiv of formaldehyde. The formation of smaller Q*n* requires reformation of the oligomer by cleavage of two adjacent methylene linkers. This process is suppressed by excess formaldehyde. The rate of ring contraction of Q8 is slow and is therefore an unlikely source of smaller Q*n*. However, Q*n* larger than Q8 are potential sources of smaller Q*n*. The trace amount of Q9 (<1%) suggests that higher homologues are unstable and break down to the more thermally stable lower homologues. However, significant amounts of Q10 (~8%) were detected and isolated. We suggest that Q10 is most likely stabilized by the encapsulation of Q5.

Generally, high reactant concentrations increase the probability of extended oligomers before ring closure occurs. High concentrations most likely have two effects on the equilibrium. They either allow sufficient time for the oligomer to reach lengths greater than the lengths required for the most commonly found Q*n* or reduce the rate at which longer oligomers are broken, thus enabling the formation of larger Q*n*. An alternative explanation for the formation of Q*n* larger than Q6 is through the insertion of additional glycoluril units (or short oligomers) into small Q*n* to form larger Q*n*. However, this mechanism seems improbable given the stability of Q5−7.

There are many equilibrium steps that could be influenced by factors such as concentration, temperature, acid type, or any combination of these. The reaction temperature and the acid concentration have a profound effect on Q*n* formation but are less important in oligomer formation. Nevertheless, these factors may be important for the stability of the oligomer. Both the reaction temperature and the concentration of H^+ ions are likely to limit the rate and the potential for the glycoluril units to invert through methylene linker disconnection. This was evident in the formation of the oligomer at 50 °C over 12 h where <2% of Q*n* was formed. In addition, no Q*n* are produced in <4 M HCl.

The basicity of the oligomer carbonyls and the accommodating nature of the concave face of the glycoluril units to a molecular or ionic guest are factors that could lower the energy difference between those oligomers that are oriented to cyclize to Q*n*, and those oriented in other ways. The array of carbonyls on the top and bottom edges of an oligomer ribbon, to which hydrogen bonding and protonation can occur, combined with the association of the cation formed with a close or a loosely hydrated counteranion could affect the thermodynamics of the oligomer closure. AM1 calculations show a significant positive electrostatic potential for the inner, concave cis-fused junction of the glycoluril moieties (Supporting Information, Table S2). This positive region will be attractive to small anions that might then stabilize a looped oligomeric structure that can close to form a Q*n* (Figure 1).

According to this model, the size of the newly formed Q*n* should be influenced by the nature of the anion guest. Evidence for anion binding in Q*n* is found in NMR spectra of Q5 in DCl/D_2O. Pure Q5 in 22% DCl/D_2O gave two similar intensity sets of resonances for both ^1H and ^{13}C NMR spectra. The intensities of these resonances were found to be markedly dependent on chloride ion concentration. One set progressively diminished as the concentration of DCl was increased to 37%. Conversely, the other set of resonances progressively diminished as the concentration was decreased to <15% DCl/D_2O. The distinct sets of resonances show the exchange rate of the DCl to be slow on the NMR time scale. Similar effects were observed for SO_4^{2-} and BF_4^-. Samples of Q5 containing these larger ions showed a relatively slow exchange with Cl^- when dissolved in DCl. We expect the binding abilities of the Q*n* cavity and the emerging cavity of an oligomer precursor to be similar. It is likely that the influences of anions and hydrogen-bonded clusters affect the balance of the competing forces of kinetics vs thermodynamics.

The catalytic solvent TsOH favors the synthesis of Q6 and Q7 (Table 2). The minimal formation of Q5 might reflect the templating effect of a hydrophobic aromatic group sitting in a relatively hydrophobic emerging cavity. Further work is being conducted in this area to fully understand the influences of anions and organic templates.

Conclusion

We expect that the number of repeat glycoluril units in Q*n* significantly impacts the properties of these macrocyclic molecules and that the newly emerging area of host−guest cucurbituril chemistry will require the ready synthesis of specific Q*n* species. This study provides a foundation for understanding the synthetic processes to form Q*n*, enabling the synthesis to be tailored to efficiently generate particular Q*n*. We have identified reaction conditions (acid concentration, acid type, temperature, and reactant concentration) that determine the relative proportions of the Q*n* produced. Manipulation of these influences allows a degree of selectivity to be achieved. A better understanding of the formation of the oligomer and the influences of anions and templates would further advance the ability to selectively synthesize any one of the Q*n*. The limit to the size of the Q*n* (isolated Q5−8 and 10, detected Q9−16) is unknown, and the factors effecting their stability and methods of synthesis are the subject of further work.

Experimental Section

General Procedures. Unless otherwise indicated, commercial materials were used as received. For ESMS, samples were dissolved in CsCl/H_2O except where specified. ^1H and ^{13}C NMR spectra were recorded in 35% DCl/D_2O at 20 °C at 300 and 80 MHz, respectively. Chemical shifts are reported in parts per million, relative to external dioxane (3.56 ppm for protons and 67.4 ppm for carbon) in D_2O. Chemical shifts were very dependent on pH and temperature. All new compounds decomposed above 250 °C. Microanalysis was performed on weight-stabilized air-dried samples except where specified. H_2O of crystallization for Q5 and Q7 was consistent with the findings for Q6.[27] The crystalline compounds Q8 and Q5@Q10 have a high capacity for incorporating H_2O into their structures. This was verified by gravimetric analysis in conjunction with desiccation.

(27) Germain, P.; Letoffe, J. M.; Merlin, M. P.; Buschmann, H. J. *Thermochim. Acta* **1998**, *315*, 87−92.

Standard Reaction Conditions for the Synthesis of Cucurbit[*n*]urils. The reactions have been carried out on a scale from 10 mg up to 1 kg. An example of isolated yields can be found in method 2 below; all others where determined by ^{13}C NMR [see Supporting Information]. For purposes of analysis, the Q*n* were recrystallized from HCl, except in the case of Q7, which was purified on Dowex 50WX2 ion-exchange resin, eluting with 1:1 1 M HCl/formic acid. Fractions were evaporated and dried at 100 °C in vacuo (0.3 mmHg) for 12 h. Cucurbit[5]uril: ^1H NMR δ 4.18 (d, 2 H, J = 15.5 Hz, CH_2), 5.15 (d, 2 H, J = 15.5 Hz, CH_2), 5.34 (s, 2 H, CH); ^{13}C NMR 51.0 (CH_2), 69.9 (CH), 157.0 (CO). Anal. Calcd for $C_{30}H_{30}N_{20}O_{10}\cdot 11H_2O\cdot HCl$: C, 32.92; H, 4.95; N, 25.60; Cl, 5.83. Found: C, 32.26; H, 4.66; N, 25.11; Cl, 5.85. Cucurbit[7]uril: ^1H NMR δ 4.00 (d, 2 H, J = 15.5 Hz, CH_2), 5.18 (d, 2 H, J = 15.5 Hz, CH_2), 5.28 (s, 2 H, CH); ^{13}C NMR 53.5 (CH_2), 72.0 (CH), 157.5 (CO). Anal. Calcd for $C_{42}H_{42}N_{28}O_{14}\cdot 8H_2O\cdot 0.5HCl$: C, 38.06; H, 4.45; N, 29.59; Cl, 1.34. Found: C, 38.17; H, 4.59; N, 29.48; Cl, 1.30. Cucurbit[8]uril: ^1H NMR δ 3.97 (d, 2 H, J = 15.5 Hz, CH_2), 5.21 (d, 2 H, J = 15.5 Hz, CH_2), 5.27 (s, 2 H, CH); ^{13}C NMR 54.5 (CH_2), 72.5 (CH), 158.0 (CO). Anal. Calcd for $C_{48}H_{48}N_{32}O_{16}\cdot 30H_2O\cdot 2.5HCl$: C, 29.41; H, 5.68; N, 22.86; Cl, 4.52. Found: C, 29.87; H, 5.15; N, 23.25; Cl, 4.64. Cucurbit-[9]uril: NMR assignments only, the compound has not been isolated; ^{13}C NMR 55.1 (CH_2), 73.3(CH). Cucurbit[5]uril@ cucurbit[10]uril: ^1H NMR δ 3.70 (d, 2 H, J = 15.5 Hz, CH_2, Q5), 4.00 (d, 2 H, J = 15.5 Hz, CH_2, Q10), 4.91 (s, 2 H, CH, Q5), 5.01 (d, 2 H, J = 15.5 Hz, CH_2, Q5), 5.30 (d, 2 H, J = 15.5 Hz, CH_2, Q10), 5.32 (s, 2 H, CH, Q10); ^{13}C NMR 50.7 (CH_2, Q5), 56.4 (CH_2, Q10), 69.3 (CH, Q5), 74.0 (CH, Q10), 156.5 (CO, Q5), 158.2 (CO, Q10). Anal. Calcd for $C_{90}H_{90}N_{60}O_{30}\cdot 28H_2O\cdot 3HCl$: C, 34.81; H, 4.83; N, 27.06; Cl, 3.42. Found: C, 34.22; H, 4.49; N, 27.19; Cl, 3.25. ESMS *m*/*z*: 1378 ($[P + 2Cs]^+$/2). ESMS data for cucurbit[*n*]urils where $n = 5-8$ can be found in Table 1. *Method 1*. To glycoluril (77 mg, 0.54 mmol) dissolved in the acid (0.4 mL) at 25−30 °C, with the aid of a sonic bath, was added formaldehyde either as a 40% aqueous solution (85 μL) or as solid paraformaldehyde (34 mg), and the solution was immediately mixed. In some cases, a gel forms after 20 min. In all cases, an exothermic reaction ensues. (On a larger scale, the reaction mixture was cooled in an ice bath during the addition of either form of formaldehyde). The mixture was heated to 100 °C for 2.5−3 h, or until the reaction was shown to be complete by NMR. Reactions on this scale were conducted in NMR tubes and analyzed as total reaction mixtures by ^{13}C NMR using D_2O as an external lock. Reactions carried out on a scale 19.5 times greater than that above were cooled and poured into MeOH (30 mL), and the precipitate was collected by vacuum filtration. After the precipitate was air-dried, the components were separated by fractional crystallization from hydrochloric acid solutions. When HCl was the solvent, it was either evaporated, and the residue was examined and purified as above, or the crystallization procedure was commenced upon cooling of the reaction mixture. *Method 2*. Finely powdered glycoluril (1000 g, 7.04 mol) and powdered paraformaldehyde (422 g, 14.07 mol) were added together and the dry powders thoroughly mixed. To this was added ice-cold concentrated HCl (1420 mL) while the mixture was stirred rapidly. Stirring was continued until the mixture set as a gel. After 30 min, the mixture was heated to 100 °C for 18 h. The composition of the total reaction mixture at this point was 9, 48, 23, 14, and 6% w/w Q5, 6, 7, 8, and 10, respectively. The mixture was cooled and filtered to collect the first crop (Z1) of colorless crystals as a composite of 10, 40, 4, 32, and 14% w/w Q5, 6, 7, 8, and 10, respectively, totaling 278 g. The filtrate was then evaporated until the volume had been reduced to one-fourth of the initial volume. To this was added water (500 mL), and the colorless crystalline suspension was collected by filtration to give 324 g (Z2) as a composite of 5, 82, 6, and 7% w/w Q5, 6, 7, and 8, respectively. The mother liquors contained Q7 as the major homologue at 59%. The volume was reduced to ~1.2 L, poured into MeOH (3.5 L), and allowed to stand at room temperature for 18 h. The off-white precipitate was collected by filtration to give 654 g (Z3). Through a repetitive process of fractionation by differential solubility and recrystallization from HCl solutions, each component was isolated in a pure form from the solid fractions Z1−3. Fractionations were achieved in 60% aqueous formic acid, which, through repetition, enabled the separation of Q8 and the Q5@Q10 complex from the other Q*n* as insoluble solids. Hot 20% aqueous glycerol was used to separate Q7 from all of the other components to achieve > 95% purity. Q7 was isolated from the aqueous glycerol by the addition of MeOH and the precipitate collected by filtration. Washing three times with MeOH × removed the glycerol, and the solid was dried at 60 °C for 12 h to give 276 g (24%) of an off-white solid. Q6 and Q5 accumulated in the formic acid soluble fractions and were separated by fractional crystallization from HCl solutions, Q6, 541 g (46%), and Q5, 94 g (8%). The formic acid insoluble Q8 and the Q5@Q10 complex were also separated by fractional crystallization from HCl solutions, Q8, 146 g (12%), and Q5@ Q10, 65 g (5%). *Method 3*. Dry, powdered glycoluril (1.02 g, 7.2 mmol) and paraformaldehyde (442 mg, 14.7 mmol) were mixed together in a paste with the addition of concentrated HCl (0.6 mL). The paste set as a solid and was then heated in a closed reaction vessel to 100 °C for 15 h with occasional manual mixing. The total reaction mixture was analyzed by ^{13}C NMR and showed weight percentages of 3, 44, 33, 12, and 8% for Q5, 6, 7, 8, and 10, respectively.

Method for Different Acids and Dilutions. Method 1 was used in all cases except where specified. In all cases, the reaction mixtures were homogeneous throughout the entire process. Q5−8 were the major products, with less than 1% of other Q*n* as determined by ^{13}C NMR. Method 1, was also used for *para*-toluenesulfonic acid except that the volume of acid was substituted for a weight of acid (10 g) and the mixture heated to 110 °C. The products were isolated by MeOH precipitation as described. The weight percentages of Q5−8 products are reported in Supporting Information, Table S4.

Chloride Binding. Pure samples of Q5 were dissolved in different concentrations of DCl/D_2O and examined by NMR. At 22% DCl/D_2O, ^1H NMR spectra showed the following: δ 4.13 (d, 2 H, J = 15.5 Hz, CH_2), 4.18 (d, 2 H, J = 15.5 Hz, CH_2), 5.28 (d, 2 H, J = 15.5 Hz, CH_2), 5.30 (d, 2 H, J = 15.5 Hz, CH_2), 5.32 (s, 2 H, CH), 5.34 (s, 2 H, CH); ^{13}C NMR δ 50.8 (CH_2), 51.1 (CH_2), 69.8 (CH), 69.9 (CH) 157.2 (CO) 157.9 (CO). From 22 to 37% DCl/D_2O, the upfield CH_2 resonance and the downfield CO resonance increase to become the only CH_2 and CO resonances observed; from 22 to 15%, the converse applies. In the ^1H NMR spectrum, the upfield resonances only are found for 37% DCl/D_2O; the converse applies for <15% DCl/ D_2O.

^{13}C-Enriched Paraformaldehyde Reaction. Method 1 was followed except for the substitution for 99% ^{13}C-enriched paraformaldehyde. In the methylene region of the ^{13}C NMR spectrum, resonances were found at 50.9, 52.4, 53.5, 54.5, 55.4, 56.8, 57.8, 58.9, and 59.9 (CH_2) ppm of approximate ratios of 7, 60, 25, 7, and <1% for each of the last 5 peaks. The remaining Q resonances were at 70.0, 71.1, 72.0, and 72.8 (CH) ppm, ~1% of the intensity of the methylene carbon.

Decamethylcucurbit[5]uril, 3. The dimethyltetracyclic ether **B** (R = Me, 5.2 g, 23.4 mmol) was placed in HCl 36% (21 mL) and H_2O (6.3 mL) and heated for 1.5 h after which all volatiles were evaporated in vacuo and the residue was examined by ^1H and ^{13}C NMR.[15] Using an external sample of dimethylglycoluril of known quantity, we determined the yield of $Me_{10}Q5$ to be 85%. ESMS of the residue gave *m*/*z* 618 [($Me_{10}Q5 + 2Cs^+$)/2, 100] and 1103 [$Me_{10}Q5 + Cs^+$, 1%].

Oligomer. Powdered glycoluril (12.2 g, 85.9 mmol) and paraformaldehyde (5.15 g, 171.8 mmol) were mixed together, and ice-cold 36% HCl (75 mL) was added with stirring. The solid material gradually dissolved, and the solution set as a clear gel that was allowed to sit at room temperature for 10 min before it was heated to 50 °C in an oil bath for 19 h. The gel produced a homogeneous solution that was poured into methanol and the resultant precipitate collected by filtration, washed with methanol, water, methanol, and ether, and air-dried for several days to give 15.4 g of colorless powder that was dried further at 80 °C in vacuo at 0.3 mmHg. Anal. Calcd for $C_6H_6N_4O_2\cdot 4H_2O$: C, 30.26; H, 5.92; N, 23.52. Found: C,

29.87; H, 5.15; N, 23.25; Cl, 0.00. ^{1}H NMR: δ 4.2−4.51 (m, methylene), 5.31−5.53 (m, methylene), 5.56 (br s, methine). The three sets of peaks had identical integrals. ^{13}C NMR: δ 52.0−55.2, 70.05−73.0, 157.5−158.5. The addition of dioxane (10 μL) resulted in a bound dioxane singlet at 2.52 ppm. In comparison with the integral of the multiplet centered at 4.36 ppm, this corresponded to ~2% w/w of Q*n*. (When 2 mol equiv of dioxane are added to a pure Q6 sample in 35% DCl, a free and a bound dioxane resonance are observed; the bound signal integrates for 1:0.77 Q6:bound dioxane. Q7 is less sensitive to dioxane as a probe, with bound dioxane resonances occurring between 2.6 and 2.75 ppm, in a ratio of 1:0.4 Q7:bound dioxane. Q5 does not bind dioxane at all.) Washing the solid oligomer (1.03 g) with boiling aqueous solutions of CsCl and filtering yielded a filtrate containing only Q5−7 (calculated from the concentration to be in total 28 mg with weight percentages of 4, 85, and 11%, respectively). Addition of dioxane to the remaining solid gave an ^{1}H NMR spectrum that was essentially unchanged and had no detectable bound dioxane signal. This oligomer sample was dissolved in formic acid and analyzed by ESMS (cone 100 V): *m*/*z* 1116.8 [($C_{35}H_{36}N_{24}O_{12}$ + Cs^+), 100%], 1129 [(Q6 + Cs^+), 32%], 1282.4 [8%], 1283.6 [($C_{41}H_{42}N_{28}O_{14}$ + Cs^+), 16%], 1284.3 [21%], 1294.9 [(Q7+ Cs^+), 41%], 1296.4 [(Q6 + Cs_2Cl), 45%], 1297.8 [21%], 1299.1 [12%], 1462.3 [(Q7 + Cs_2Cl), 10%], 1463.9 [9%], 1793.5 [(Q10 + Cs^+), 3%].

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Supporting Information Available: HyperChem 6.0.1 gas-phase AM1 heats of formation (ΔH_f, kcal/mol) for cucurbit[*n*]urils, Q*n*, and methylated cucurbit[*n*]urils, Me_{2n}Q*n*, *n* = 3−10 after geometry optimization; MacSpartan Pro AM1 geometry optimizations of glycoluril−formaldehyde trimers with terminal diether bridges; ^{13}C NMR chemical shifts (ppm) of the three carbons of the cucurbit[*n*]urils, *n* = 5−8, in 1:1 v/v D_2O/concentrated DCl; dependence of the methylene and methine ^{13}C NMR chemical shifts on the number of repeat units, *n*, in cucurbit[*n*]urils; and the effects of varying acid type and acid concentration on the weight percentages of Q5−8 products. This material is available free of charge via the Internet at http://pubs.acs.org.

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