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Methylene-Bridged Glycoluril Dimers: Synthetic Methods

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Methylene-bridged glycoluril dimers are the fundamental building blocks of cucurbituril (**CB**[6]), its homologues (**CB**[*n*]), and its derivatives. This paper describes three complementary methods for the synthesis of C- and S-shaped methylene-bridged glycoluril dimers (**29**−**34** and **37**−**44**). For this purpose, we prepared glycoluril derivatives (**1a**−**d**) bearing diverse functionalities on their convex face. These glycoluril derivatives were alkylated under basic conditions (DMSO, *t*-BuOK) with 1,2-bis(halomethyl)aromatics **6**−**15** to yield **4a**−**d** and **16**−**24**, which contain a single aromatic *o*-xylylene ring and potentially nucleophilic ureidyl NH groups. Glycoluril derivatives bearing potentially electrophilic cyclic ether groups (**5a**−**f**) and **25**−**28** were prepared by various methods including condensation reactions in refluxing TFA containing paraformaldehyde. The condensation reactions of **4a**−**d** and **16**−**24** with paraformaldehyde under anhydrous acidic conditions (PTSA, $ClCH_2CH_2Cl$, reflux) give, in most cases, the C-shaped and S-shaped methylene-bridged glycoluril in good to excellent yields. In many cases, the C-shaped compound is formed preferentially with high diastereoselectivity. Cyclic ethers **5a**,**d**−**f** and **25**−**26** undergo highly diastereoselective dimerization reactions to yield methylene-bridged glycoluril dimers with the formal extrusion of formaldehyde. Last, it is possible to perform selective heterodimerization reactions using both cyclic ethers and glycoluril derivatives bearing ureidyl NH groups. These reactions deliver the desired C- and S-shaped heterodimers with low to moderate diastereoselectivities. This heterodimerization route is the method of choice in cases where the homodimerization reactions fail. The formation of side products (±)-**35b** and (±)-**35d** helps clarify the electronic requirements for a successful **CB**[*n*] synthesis. The X-ray structures of **30*C***, **38*C***, and **38*S*** allow for a discussion of the structural features of this class of compounds.

Introduction

Cucurbituril (**CB**[6]) is a an intriguing macrocyclic compound comprising six glycoluril (**1f**) rings and twelve methylene bridges whose structure was established by Mock in 1981.[1] **CB**[6] possesses a hydrophobic cavity with carbonyl-lined portals that results in remarkable molecular recognition properties (Chart 1). For example, Mock and co-workers found that **CB**[6] binds tightly ($K_d \approx 1$ μM) to alkyldiammonium ions in aqueous solution by a combination of the hydrophobic effect and ion−dipole interactions.[2] It was also demonstrated that **CB**[6] is an efficient enzyme mimic capable of catalyzing the dipolar cycloaddition between azide and acetylene-derivatized ammonium ions by their simultaneous binding within the cavity of **CB**[6].[3] The synthetic method used to prepare cucurbituril is equally impressive; simply heating glycoluril (**1a**) and formaldehyde under strongly acidic conditions (H_2SO_4, 135−145 °C) results in the formation of **CB**[6] in high yield.[4] This straightforward synthetic method has allowed the use of **CB**[6] in many elegant studies including molecular necklaces,[5] bowls,[6] polyrotaxanes,[7] DNA complexes,[8] molecular switches,[9] removal of contaminants from aqueous waste streams,[10] studies of molecular polarizability,[11] and ion and molecular complexation studies.[2,12]

In efforts to expand the range of applications, several groups have been investigating the preparation of congeners of cucurbituril that display enhanced properties. This line of inquiry was first pursued by Stoddart, who prepared Me_{10}**CB**[5] by condensation of **1e** with formaldehyde.[13] More recently, Kim and co-workers[14,15] as well as Day and co-workers[16,17] isolated homologues of cucurbituril comprising five, seven, eight, and ten glycoluril

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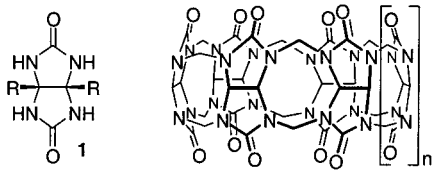
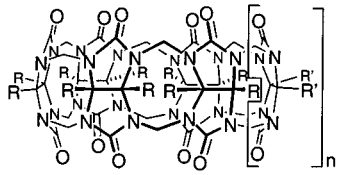
CHART 1



1a R = CO_2Et
1b R = Ph
1c R = 2-pyridyl
1d R,R = $(CH_2)_4$
1e R = Me
1f R = H

CB[5] (n = 0)
CB[6] (n = 1)
CB[7] (n = 2)
CB[8] (n = 3)
CB[10] (n = 5)



Me_{10}**CB**[5] (R = Me, n = 0)
Cy_5**CB**[5] (R,R = R', R' = $(CH_2)_4$, n = 0)
Cy_6**CB**[6] (R,R = R',R' = $(CH_2)_4$, n = 1)
Ph_2**CB**[6] (R = H, R' = Ph, n = 1)

units (**CB**[5], **CB**[7], **CB**[8], and **CB**[10]) and detected other homologues by performing the condensation reaction under milder, kinetically controlled conditions. These advances have already expanded the range of molecular recognition applications[18−20] of these systems to include molecular Russian dolls,[21] ball bearings,[22] gyroscopes,[17b] the catalysis of a [2 + 2] photoreaction,[23] and the selective recognition of a charge-transfer complex.[24] Most recently, Kim's group has demonstrated that cyclohexyl-fused glycoluril **1d** is transformed into Cy_5**CB**[5] and Cy_6**CB**[6][25] whereas Nakamura's group isolated the partially substituted Ph_2**CB**[6].[26]

We have also been interested in tailoring the recognition properties of **CB**[*n*] by preparing derivatives functionalized around their equator, at their methylene bridges, or by substitution of an aromatic ring for a glycoluril ring. In contrast to the one-step syntheses of Stoddart, Kim, and Day, we have chosen to pursue a multistep synthetic approach. Such an approach, while inherently more labor intensive, affords greater structural control, may generate mechanistic insights that result in cucurbituril syntheses with enhanced scope, and offers the opportunity to study the self-assembly and molecular recognition properties of intermediates enroute to congeners of cucurbituril.[27] Our approach[28] to the synthesis of congeners of **CB**[6] relies on the identification of the methylene-bridged glycoluril dimer substructure (**2**, bold in **CB**[6]) as the essential building block for cucurbituril derivatives (Scheme 1). In this paper we present three complementary synthetic routes to methylene-bridged glycoluril dimers. We also present the X-ray crystallographic characterization of these two diastereomers.

Results and Discussion

Experimental Design. To develop flexible methods for the synthesis of derivatives of **CB**[*n*], we have initially focused our attention on the preparation of methylene-bridged glycoluril dimers (**2*C*** and **2*S***) which constitute

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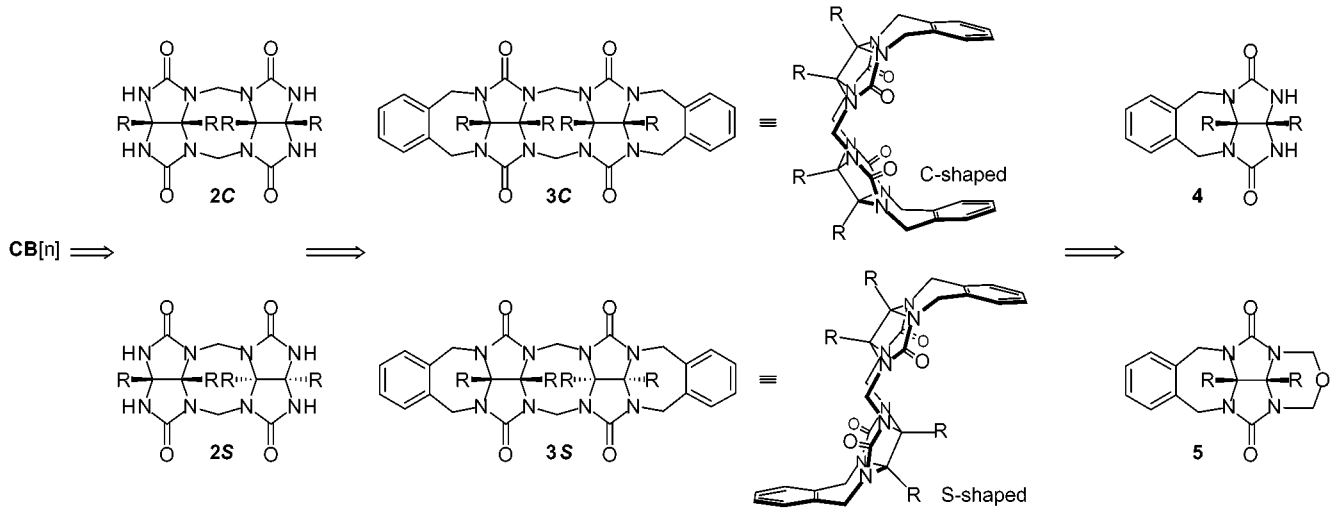
SCHEME 1. Retrosynthetic Analysis of CB[*n*]



the fundamental structural unit of cucurbituril (Scheme 1). To minimize the synthetic challenges posed by the presence of four ureidyl NH groups in **2*C*** and **2*S***, we further restrict the present study to the preparation of derivatives of **2*C*** and **2*S*** comprising a single set of methylene bridges and bearing two *o*-xylylene groups (**3*C*** and **3*S***). We use the suffixes ***C*** and ***S*** throughout this paper to distinguish between these two diastereomers because their three-dimensional structures resemble those letters (Scheme 1). A successful synthesis of congeners of cucurbituril requires control over the relative stereochemistry of each pair of methylene-bridged glycoluril dimers. For example, consideration of the pair of diastereomers **3*C*** and **3*S*** reveals that only the C-shaped diastereomer **3*C*** is capable of being transformed into a derivative of cucurbituril, since the S-shaped diastereomer **3*S*** possesses the wrong relative stereochemistry. An important objective of the present work, therefore, is the development of methods that allow the diastereoselective formation of **3*C***. Our retrosynthetic analysis of **3*C*** and **3*S*** leads to ureidyl NH compound **4** and cyclic ether **5**. We envisioned that condensation reactions between **4** and **5** would proceed under acidic conditions where the nucleophilic tautomer of **4** could react with the iminium ion generated after protonation of **5**. To investigate the scope and limitations of the dimerization reaction used to prepare methylene-bridged glycoluril dimers, we needed to prepare derivatives of **4** and **5** bearing a range of solubilizing substituents on their convex faces and on their aromatic rings.

Synthesis of Glycoluril Building Blocks. Compounds **1a**−**d** were prepared by literature procedures.[29−33] We chose these four building blocks because (1) they were easily prepared, (2) they broadly represented the range of glycoluril derivatives typically encountered (alkyl, carboxylic acid derivative, aromatic, and heteroaromatic), and (3) they provided good solubility characteristics. The majority of glycoluril derivatives used in this paper, however, are derived from **1a**, which possesses two ethyl ester groups on its convex face. This choice is based on our interest in preparing water soluble methylene-bridged glycoluril dimers[27,34] and the fact that glycoluril derivatives bearing ethoxycarbonyl groups dimerize in high yield.

Synthesis of 1,2-Bis(halomethyl)aromatic Compounds. In their pioneering studies of molecular recognition, self-assembly, and catalysis, the groups of Nolte[35,36] and Rebek[37,38] have devised many practical synthetic methods for the preparation of derivatives of glycoluril. An important step in many of these syntheses involves the nucleophilic addition of glycoluril anions to 1,2-bis(halomethyl)aromatics to generate glycoluril derivatives bearing *o*-xylylene rings on one or both sides of the glycoluril skeleton.[39] Chart 2 shows the structures of 10 alkylating agents (**6**−**15**) that we have used in our synthetic studies. Of these 10 alkylating agents, **6** and **14** were commercially available, **7**,[40] **8**,[41,42] **10**,[43] **11**,[44] and **15**[45] were prepared by literature procedures, and **9**, **12**,

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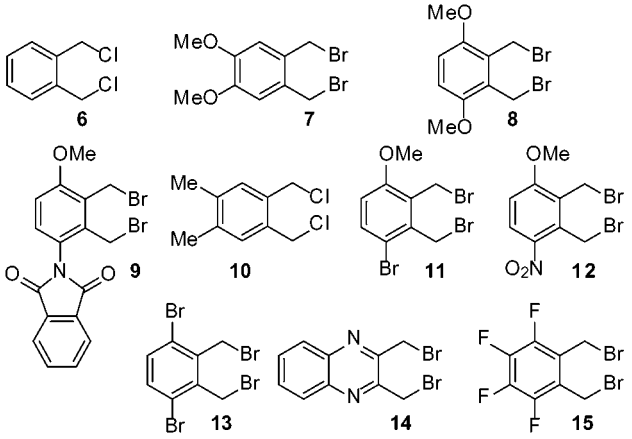
CHART 2



and **13** were prepared by bromination of the corresponding *o*-xylylene derivatives with *N*-bromosuccinimide in CCl_4.[46,47]

Synthesis of Glycoluril Derivatives Bearing Two Ureidyl NH Groups and a Single *o*-Xylylene Group. For the preparation of glycoluril derivatives bearing a single substituted *o*-xylylene sidewall, we adapted chemistry developed by the groups of Rebek and Nolte.[39] Treatment of glycoluril derivatives **1a**−**d** with *t*-BuOK in DMSO results in nucleophilic species that react with bis(halomethyl)aromatics **6**−**15** yielding glycoluril derivatives **4a**−**d** and **16**−**24** (Chart 3 and Table 1) in low to moderate yields. Entries 1−4 (Table 1) illustrate the effect of the four different solubilizing groups (CO_2Et, Ph, 2-pyridyl, and $(CH_2)_4$) on the alkylation reaction with a single alkylating agent (**6**). The nature of the solubilizing group significantly affects the yield of the alkylation reaction, and in our hands, the alkylation of **1a** proceeds most smoothly, since the anion generated by treatment with *t*-BuOK is nicely soluble in DMSO and shows a lower tendency to form gels which lower yields significantly. Entries 1 and 5−13 illustrate the effect of the alkylating agent on the alkylation reaction; compounds **16**−**24** have been arranged from electron rich to electron poor. The electronic nature of the substituents on the aromatic ring does not have a discernible effect on the efficiency of the alkylation reaction, although we have noticed that extended reaction times lead to decreased yields in the case of the more electron deficient alkylating agents. Compounds (±)-**18**, (±)-**20**, and (±)-**21** are chiral because of the unsymmetrical arrangements of functional groups on their aromatic rings; these compounds are synthesized and used in this paper as the racemic mixture.

Synthesis of Cyclic Ethers by Acid-Catalyzed Condensation with Paraformaldehyde. Having secured a range of potentially nucleophilic glycoluril derivatives (**4a**−**d** and **16**−**24**) bearing a range of solubilizing groups on their convex faces and substituents on their aromatic rings, we turned to the problem of creating a series of potentially electrophilic glycoluril derivatives (**5a**−**f** and **25**−**28**). For this purpose, we turned to the work of Nolte, who has developed a methodology utilizing glycoluril-derived cyclic ethers, chloromethyl groups, acetoxymethyl groups, and hydroxymethyl groups for the generation of iminium ions that undergo efficient electrophilic aromatic substitution reactions.[48−52] For our purposes, the more stable cyclic ethers (Chart 4) were preferable. The Nolte cyclic ether synthesis[53] calls for sequential treatment with NaOH and formaldehyde in aq DMSO, followed by reflux in HCl at pH 1. We anticipated that these basic and aqueous acidic conditions might pose problems with substrates bearing ethoxycarbonyl groups. We, therefore, developed a one-step procedure that proceeds under anhydrous acidic conditions (TFA, reflux) using paraformaldehyde (Table 2). These reactions proceed in moderate to good yield and offer an alternative to Nolte's procedure when working with compounds containing potentially sensitive functional groups. The lowest yield (20%) was obtained for 2-pyridyl-substituted glycoluril **5c**. This result is not surprising, since the pyridyl ring is protonated in TFA, which probably raises the energy of the intermediates leading to **5c**, resulting in a reduced reaction rate or side reactions.

Synthesis of Methylene-Bridged Glycoluril Dimers. After preparing a series of glycoluril derivatives bearing potentially nucleophilic ureidyl NH groups (**4a**−**d** and **16**−**24**) and potentially electrophilic cyclic ether groups (**5a**−**f** and **25**−**28**), we turned our attention toward their condensation reactions that lead to methylene-bridged glycoluril dimers. Chart 5 gives a summary of the compounds (**29*C***−**44*C*** and **29*S***−**44*S***) that are discussed in this paper. There are three synthetic methods that lead from the two sets of building blocks to methylene-bridged glycoluril dimers: (1) the reaction of 2 equiv of **4** with a source of formaldehyde, (2) the condensation of **4** with cyclic ether **5**, and (3) the reaction of 2 equiv of **5** with the formal extrusion of formaldehyde. In each case, we propose that the reaction proceeds through a common set of intermediates (Scheme 2), although many subtle variations are possible and we do not have evidence to exclude those possibilities in this discussion. Compound **4** can tautomerize into nucleophile (±)-**45**, which after reaction with formaldehyde, proton transfer, loss of water, and tautomerization leads to the racemic mixture (±)-**47**. Similarly, protonation of cyclic ether **5** followed by extrusion of formaldehyde also leads to racemic mixture (±)-**47**. At this stage, two different scenarios are possible: **47** can react with a molecule of like handedness (**45**) or it can react with a molecule of opposite handedness (*ent*-**45**). Reaction between **47** and **45** gener-

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(53) Niele, F. G. M.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1988**, *110*, 172−177.

CHART 3

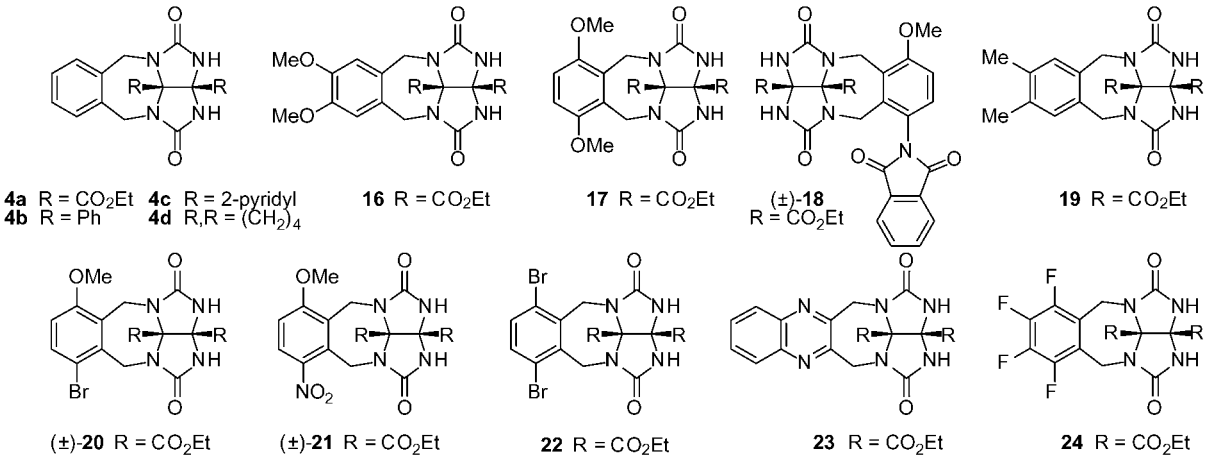
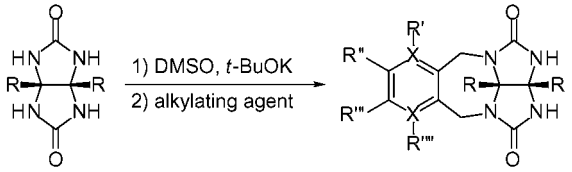


TABLE 1. Synthesis of 4b−d and 16−24



entry	R	alkylating agent	product	yield (%)
1	CO_2Et	**6**	**4a**	84[a]
2	Ph	**6**	**4b**	62
3	2-pyridyl	**6**	**4c**	43
4	$(CH_2)_4$	**6**	**4d**	31
5	CO_2Et	**7**	**16**	45
6	CO_2Et	**8**	**17**	47
7	CO_2Et	**9**	**18**	22
8	CO_2Et	**10**	**19**	68
9	CO_2Et	**11**	**20**	62
10	CO_2Et	**12**	**21**	32
11	CO_2Et	**13**	**22**	37
12	CO_2Et	**14**	**23**	26
13	CO_2Et	**15**	**24**	45

[a] Ref 39a.

ates intermediate **48*S***, which is transformed into **49*S*** and ultimately into the S-shaped product **3*S***. Conversely, reaction between **47** and *ent*-**45** generates intermediate **48*C***, which leads to the C-shaped methylene-bridged glycoluril dimer via intermediate **49*C***. Since a highly diastereoselective reaction is not expected between intermediates **45** and **47**, one would expect to isolate a mixture of the S-shaped and C-shaped methylene-bridged glycoluril dimers if the reaction is run under kinetically controlled conditions. If, however, the reaction is run under thermodynamically controlled conditions, the ratio of the two products will be dictated solely by the relative free energies of the S- and C-shaped diastereomers.

Homodimerization Reactions of Ureidyl NH Compounds. The most straightforward synthesis of methylene-bridged glycoluril dimers involves the condensation reaction between 2 equiv of **4** and 2 equiv of formaldehyde. Our standard procedure (Scheme 3) involves heating the reactants at reflux in 1,2-dichloroethane containing *p*-toluenesulfonic acid as acid catalyst under anaddition funnel filled with molecular sieves for at least 1 day. Table 3 summarizes 12 homodimerization reactions that we have performed. In all cases, we observe a moderate

CHART 4

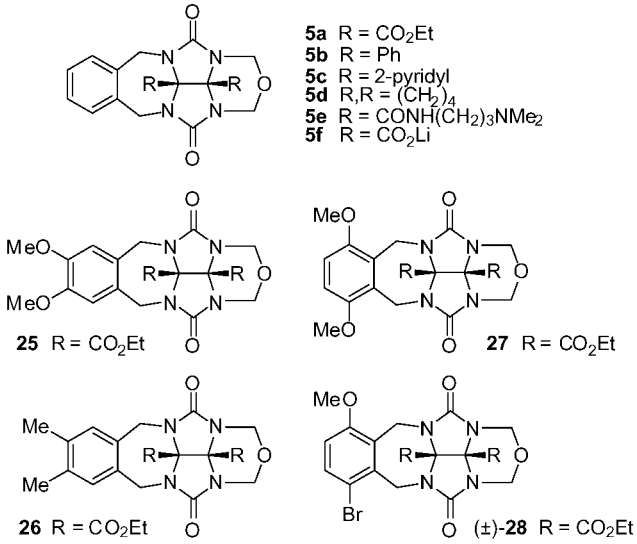
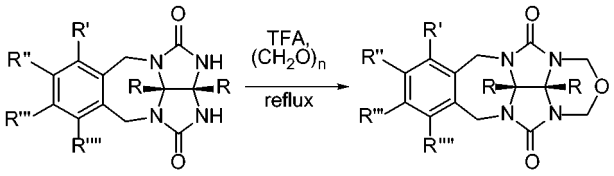


TABLE 2. Synthesis of Cyclic Ethers under Anhydrous Acidic Conditions

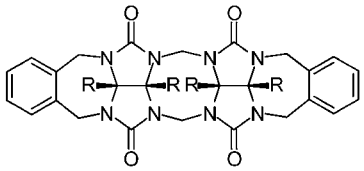


entry	R	starting material	product	yield (%)
1	CO_2Et	**4a**	**5a**	44
2	2-pyridyl	**4c**	**5c**	20
3	$(CH_2)_4$	**4d**	**5d**	63
4	CO_2Et	**16**	**25**	52
5	CO_2Et	**17**	**27**	56
6	CO_2Et	**19**	**26**	55
7	CO_2Et	**20**	**28**	34

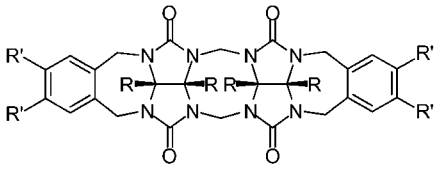
to large preference for the formation of the C-shaped diastereomers. Such a preference, if general, would explain the high yields obtained in the synthesis of **CB**[*n*].

Entries 1−4 (Table 3) illustrate the pronounced influence of the solubilizing groups on the convex face of the glycoluril ring on the dimerization reaction. For example,

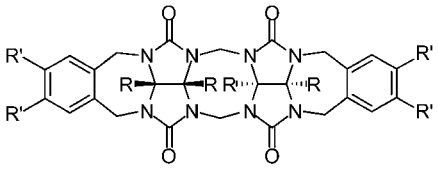
CHART 5. Chemical Structures of Methylene-Bridged Glycoluril Dimers



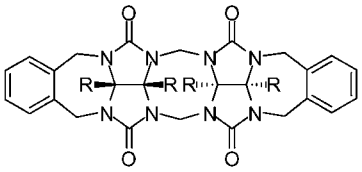
29*C* R = CO_2Et
30*C* R = Ph
31*C* R = 2-pyridyl
32*C* R,R = $(CH_2)_4$
33*C* R,R = $(CO)_2N(CH_2)_3NMe_2$
34*C* R = CO_2H



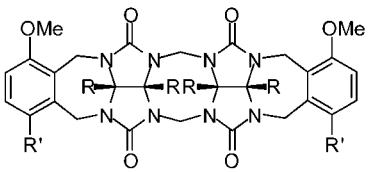
37*C* R = CO_2Et, R' = OMe
38*C* R = CO_2Et, R' = Me



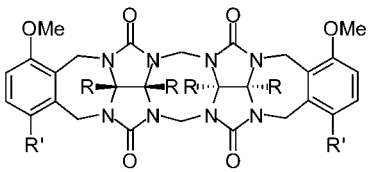
37*S* R = CO_2Et, R' = OMe
38*S* R = CO_2Et, R' = Me



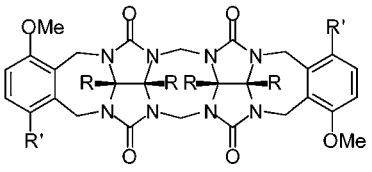
29*S* R = CO_2Et
30*S* R = Ph
31*S* R = 2-pyridyl
32*S* R,R = $(CH_2)_4$
33*S* R,R = $(CO)_2N(CH_2)_3NMe_2$
34*S* R = CO_2H



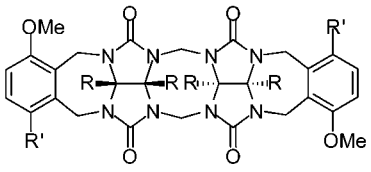
39*C* R = CO_2Et, R' = OMe
40*CC* R = CO_2Et, R' = Br
41*CC* R = CO_2Et, R' = NO_2



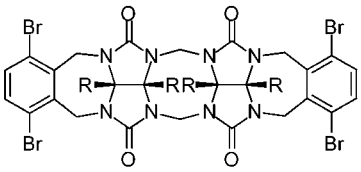
39*S* R = CO_2Et, R' = OMe
(±)-**40*SC*** R = CO_2Et, R' = Br
(±)-**41*SC*** R = CO_2Et, R' = NO_2



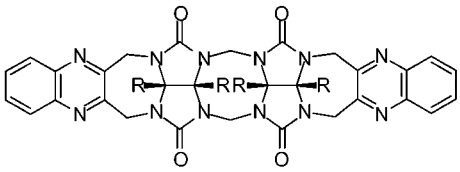
(±)-**40*CT*** R = CO_2Et, R' = Br
(±)-**41*CT*** R = CO_2Et, R' = NO_2



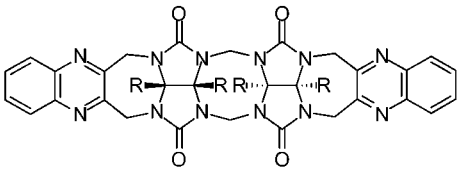
40*ST* R = CO_2Et, R' = Br
41*ST* R = CO_2Et, R' = NO_2



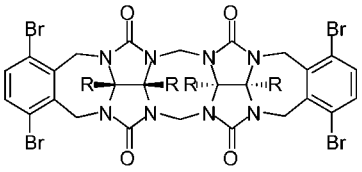
42*C* R = CO_2Et



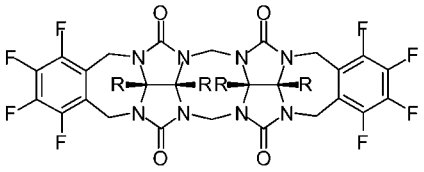
43*C* R = CO_2Et



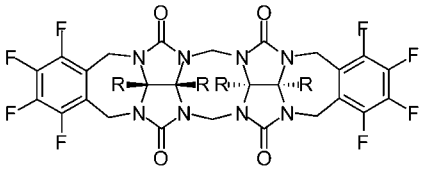
43*S* R = CO_2Et



42*S* R = CO_2Et



44*C* R = CO_2Et



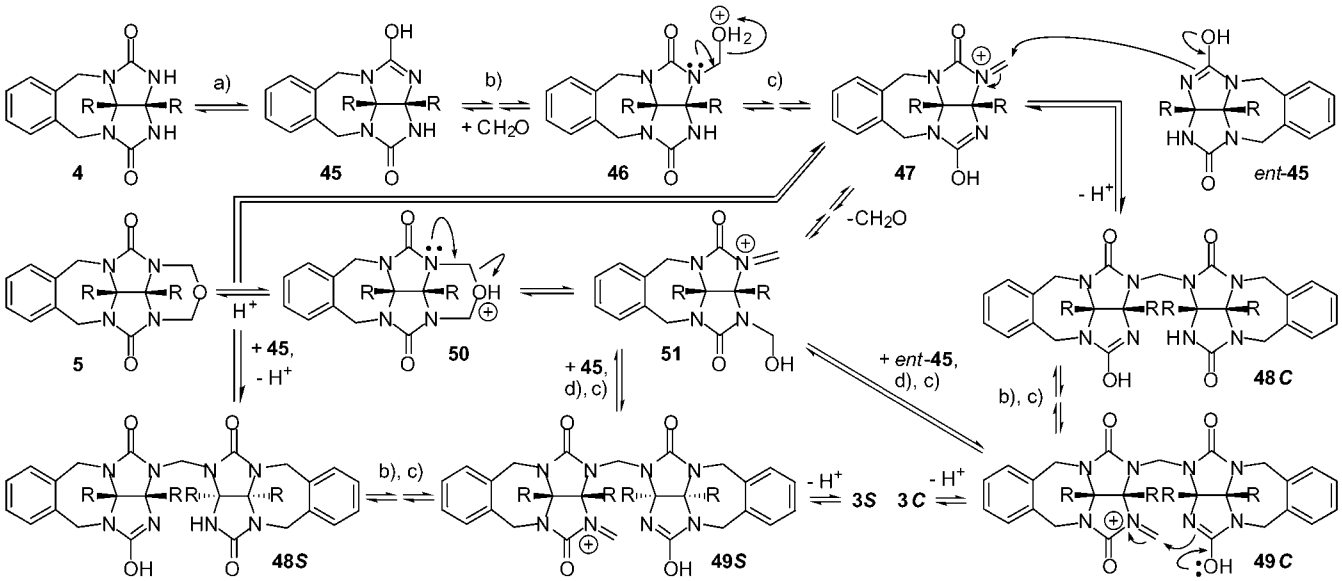
44*S* R = CO_2Et

the dimerization reaction with ethoxycarbonyl-substituted glycoluril **4a** (entry 1) furnishes only the C-shaped diastereomer **29*C***, whereas cyclohexyl- and phenyl-substituted glycolurils **4d** and **b** (entries 4 and 2) proceed in lower yield and with the formation of side products **35** and **36**. For **4c**, with 2-pyridyl solubilizing groups, we did not detect either **31*C*** or **31*S*** by ^1H NMR. These changes in yield and product distribution cannot be explained by steric differences. Below, we present a mechanistic rationale for these changes based on the electronic nature of the solubilizing groups.

The remaining entries in Table 3 focus on the chemistry of glycoluril derivatives bearing ethoxycarbonyl solubilizing groups, since those substrates result in efficient dimerization reactions. Entries 5 and 7−12 illustrate that the dimerization reaction tolerates a variety of different substituents on their aromatic rings (OMe, Br, NO_2, F, and heteroaromatics). The nature and location of substituents can, however, significantly influence the rate and yield of the reaction. For example, simply changing the location of two methoxy groups (compare entries 5 and 6) resulted in decomposition rather than dimerization, and the presence of a quinoxaline ring (entry 11) lowers the yield and greatly reduces the reaction rate presumably because of the protonation of the quinoxaline ring N-atom.

As mentioned above, compounds (±)-**20** and (±)-**21** are chiral and racemic because of the unsymmetrical arrangements of substituents on their *o*-xylylene rings. In the dimerization reaction of (±)-**21** (Table 3, entries 9), two C-shaped and two S-shaped diastereomers were isolated and characterized. We denote these compounds as **41*CC*** (*C*-shaped, OMe groups *cis*), (±)-**41*CT*** (*C*-shaped, OMe groups *trans*), (±)-**41*SC*** (*S*-shaped, OMe groups *cis*), and **41*ST*** (*S*-shaped, OMe groups *trans*). Compounds **41*CC*** and **41*ST*** result from the dimerization of two molecules of opposite handedness and are achiral *meso* compounds, whereas the racemic mixtures (±)-

SCHEME 2. Outline of Three Pathways to Methylene-Bridged Glycoluril Dimers[a]



[a] Mechanistic steps: (a) tautomerization, (b) nucleophilic addition (+CH_2O) and proton transfer, (c) loss of water and tautomerization, (d) proton transfer.

SCHEME 3. Dimerization of Glycoluril Derivatives with Ureidyl NH Compounds

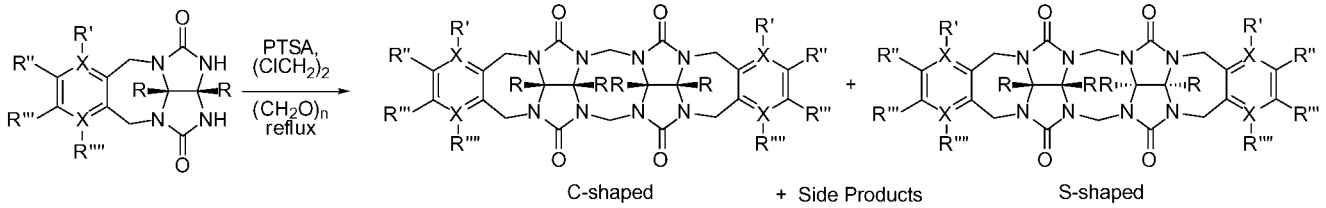
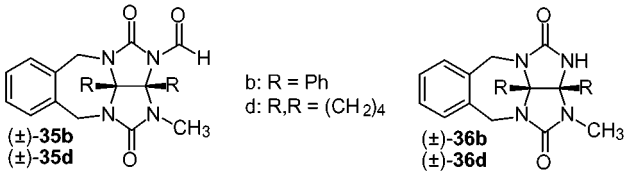


TABLE 3. Dimerization of Glycoluril Derivatives Bearing Ureidyl NH Groups

entry	R	starting material	C-shaped (yield, %)		S-shaped (yield, %)		side product(s) (yield, %)
1	CO_2Et	**4a**	**29*C***	(88)	**29*S***	(nd)	
2	Ph	**4b**	**30*C***	(19)	**30*S***	(nd)	**35b** (26), **36b** (2)
3	2-pyridyl	**4c**	**31*C***	(nd)[a]	**31*S***	(nd)	
4	$(CH_2)_4$	**4d**	**32*C***	(57)	**32*S***	(nd)	**35d** (9), **36d** (5)
5	CO_2Et	**16**	**37*C***	(87)	**37*S***	(nd)	
6	CO_2Et	**17**	**39*C***	(nd)	**39*S***	(nd)	
7	CO_2Et	**19**	**38*C***	(75)	**38*S***	(6)	
8	CO_2Et	**20**	**40*CC***	(46)	**40*SC***	(nd)	
			40*CT*	(48)	**40*ST***	(nd)	
9	CO_2Et	**21**	**41*CC***	(28)	**41*SC***	(21)	
			41*CT*	(24)	**41*ST***	(22)	
10	CO_2Et	**22**	**42*C***	(47)	**42*S***	(10)	
11	CO_2Et	**23**	**43*C***	(35)	**43*S***	(18)	
12	CO_2Et	**24**	**44*C***	(44)	**44*S***	(3)	

[a] nd = not detected.



41*CT* and (±)-**41*SC*** result from the dimerization of **21** of like handedness. In this example, a nearly statistical distribution of the four stereoisomers was obtained. In contrast, the dimerization of (±)-**20** yielded exclusively the C-shaped diastereomers **40*CC*** and (±)-**40*CT*** in 94% combined yield.

Separation, Identification, and X-ray Crystallographic Characterization of the C-Shaped and S-Shaped Diastereomers. Gratifyingly, the separation of the crude reaction mixtures described in Table 3 was possible using simple silica gel chromatography. The conformationally rigid C-shaped diastereomers have higher dipole moments, lower R_f values, and lower solubilities in common organic solvents than the corresponding S-shaped diastereomers ($\mu = 0$ D by symmetry arguments), which facilitate their purification. Spectroscopic identification of the C-shaped and S-shaped diastereomers is based on a combination of ^{1}H and ^{13}C NMR spectroscopy and symmetry arguments. Consider, for example, the C-shaped and S-shaped diastereomers **38*C*** and **38*S*** (Table 3, entry 7). The C-shaped diastereomer **38*C*** is C_{2v}-symmetric, whereas **38*S*** has time-averaged C_{2h}-symmetry. These symmetry differences manifest themselves in the number of resonances expected for the newly formed methylene bridges; for **38*C*** we expect and observe a pair of doublets for the diastereotopic methylene protons (6.02 and 4.58 ppm), whereas for **38*S*** we expect and observe a singlet (5.00 ppm) for the chemically equivalent methylene protons. These symmetry considerations are sufficient to allow complete spectroscopic identification of methylene-bridged glycoluril dimers prepared from two achiral building blocks. A peculiar but particularly diagnostic feature of the ^{1}H NMR spectra of

all of the S-shaped diastereomers that we have prepared to date is the significant upfield shift observed for only one of the two chemically nonequivalent CH_2 groups of the $CO_2CH_2CH_3$ solubilizing groups. For example, for **38*S*** the two methylene groups resonate at 4.19 and 3.58 ppm, whereas for **38*C*** both resonate at 4.17 ppm. The X-ray crystal structure of **38*S*** (Figure 1) provides an explanation for this observation. In each of two rapidly equilibrating S-shaped conformations of **38*S***, one of the methylene groups of the internal CO_2Et groups is in the shielding region of the aromatic ring of the opposing sidewall, leading to the observed upfield shift. A similarly diagnostic feature of the S-shaped versus the C-shaped diastereomers is the ^{13}C NMR chemical shifts of the central methylene bridges. For **38*C*** these carbon atoms resonate at 47.8 ppm, whereas for **38*S*** they resonate at 51.8 ppm. In general, the C-shaped diastereomers resonate at ≈47−48 ppm, and the S-shaped diastereomers resonate at 51−52 ppm.[17] These three criteria and symmetry arguments allow complete structural assignments of even the most complicated C_s-, C_2-, and C_1-symmetric methylene-bridged glycoluril dimers (examples: **41*CC***, (±)-**41*CT***, (±)-**41*SC***, and **41*ST***).

The structural assignments of the C-shaped and S-shaped diastereomers based on ^1H and ^{13}C NMR and symmetry arguments described above have been further corroborated by X-ray crystallography of many of our compounds. Figure 1 shows the X-ray structures determined for **30*C***, **38*C***, and **38*S***. Compounds **30*S*** and **38*C*** assume C-shaped conformations with their *o*-xylylene rings roughly parallel. All four solubilizing groups (Ph and CO_2Et) are displayed on one face of the molecule, resulting in an amphiphilic topology. Compound **38*C*** crystallized as the CH_3CN solvate; one of the solvating CH_3CN molecules fills its cleft with the CH_3 group oriented toward the glycoluril rings. The distances between the centers of the *o*-xylylene rings of **30*C*** and **38*C***, defined as the C1−C2−C3−C4−C4A−C18A and C9A−C10−C11−C12−C13−C13A centroids, are 7.366 and 7.588 Å, respectively. Because of the slight tapering of the cleft, the distances between the tips of the *o*-xylylene rings, defined as the distance between the centroids of the C2−C3 and C11−C12 bonds, are 6.951 and 7.258 Å for **30*C*** and **38*C***, respectively. The mean planes of the aromatic rings of **30*C*** and **38*C*** intersect each other with angles of 21.8° and 17.1°, respectively. There is a slight overall end-to-end twist of the C-shaped molecules of **30*C*** (−4.0°) and **38*C*** (−3.3°), as measured by the dihedral angle through the centroids of the C2−C3, C4A−C18A, C9A−C13A, and C11−C12 bonds. The substituents on the convex face of **30*C*** and **38*C*** are nearly eclipsed; the C5B−C5A−C6A−C6B and C7B−C7A−C8A−C8B dihedral angles measure 9.6° and 3.4° (**30*C***) and −1.6° and 1.4° (**38*C***), respectively. The substituents at C6A and C7A on the convex face of the molecules are nearly collinear; the C6B−C6A−C7A and C7B−C7A−C6A angles amount to 95.0° and 94.7° (**30*C***) and 96.5° and 95.0° (**38*C***), respectively. The separations between these substituents, as measured by the C6B−C7B distance, are 3.985 Å (**30*C***) and 3.984 Å (**38*C***), indicating that they are not in van der Waals contact. The N6−C7−N7 and N16−C16−N15 bond angles of the methylene bridges amount to 116.2° and 118.3° (**30*C***) and 114.8° and 115.0° (**38*C***). These values are larger than the tetrahedral bond angle, as are those observed for Me_{10}**CB**[5] (114.0°−115.4°)[13] and **CB**[5] (113.2°−114.7°), **CB**[6] (112.9°−

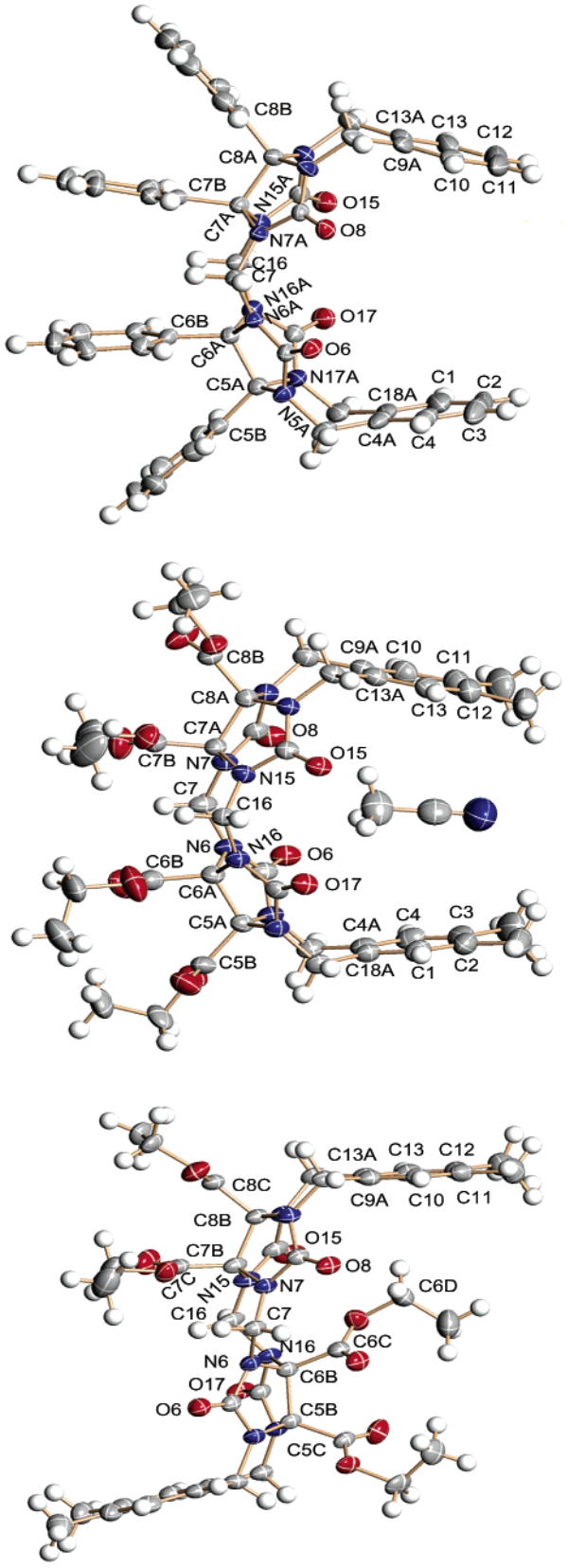


FIGURE 1. X-ray crystal structures of **30*C***, **38*C***, and **38*S***. The solvating $CHCl_3$ and toluene molecules have been removed from the structure of **30*C***.

SCHEME 4. Dimerization Reactions of Glycoluril-Derived Cyclic Ethers

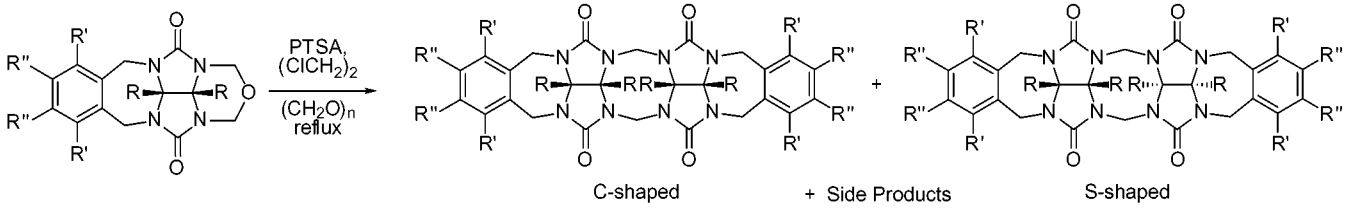


TABLE 4. Dimerization Reactions of Glycoluril-Derived Cyclic Ethers

entry	R	starting material	C-shaped (yield, %)		S-shaped (yield, %)		side product(s) (yield, %)
1	CO_2Et	**5a**	**29*C***	(92)	**29*S***	(nd)	
2	Ph	**5b**	**30*C***	(nd)[a]	**30*S***	(nd)	**35b** (42)
3	2-pyridyl	**5c**	**31*C***	(nd)	**31*S***	(nd)	
4	$(CH_2)_4$	**5d**	**32*C***	(34)	**32*S***	(nd)	**35d** (16), **36d** (12)
5	$CONH(CH_2)_3NMe_2$	**5e**	**33*C***	(85)	**33*S***	(nd)	
6	CO_2Li	**5f**	**34*C***	(85)	**34*S***	(nd)	
7	CO_2Et	**25**	**37*C***	(93)	**37*S***	(nd)	
8	CO_2Et	**26**	**38*C***	(87)	**38*S***	(3)	
9	CO_2Et	**27**	**39*C***	(nd)	**39*S***	(nd)	

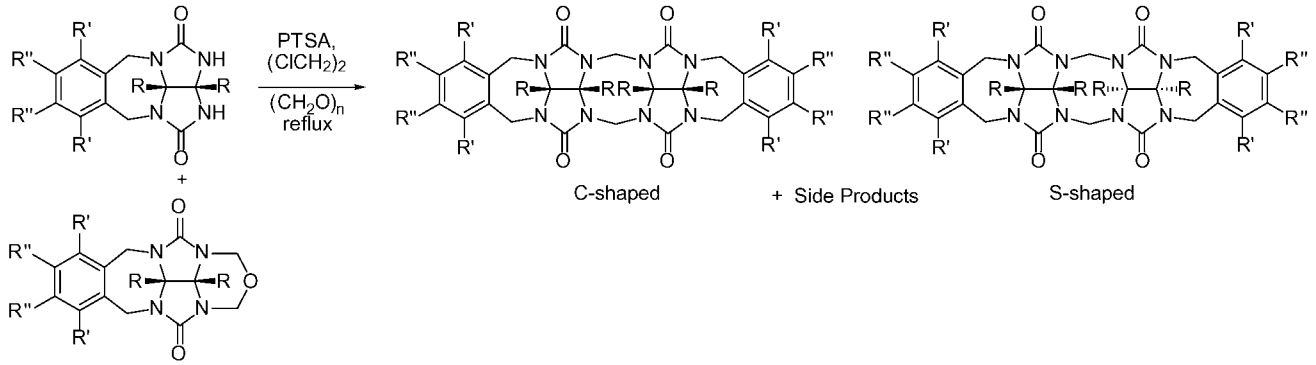
[a] nd = not detected.

115.0°), **CB**[7] (112.7°−114.5°), and **CB**[8] (113.0°−113.6°).[1,15] The ureidyl N atoms involved in the central eight-membered ring do not show significant deviations from planarity; the sum of the three bond angles around N6A, N7A, N15A, and N16A of **30*C*** amount to 358.3°, 359.9°, 359.5°, and 359.8°, whereas those around N6, N7, N15, and N16 of **38*C*** amount to 359.0°, 359.9, 359.0°, and 360°, respectively. The distances between the carbonyl oxygens (O6−O17 and O8−O15) of a single glycoluril ring are 5.611 and 5.653 Å (**30*C***) and 5.755 and 5.785 (**38*C***), distances that are slightly larger than those observed for related molecules containing a single glycoluril ring[48−50] but smaller than those observed for **CB**[5] (6.176−6.217 Å), **CB**[6] (5.98−6.042 Å), **CB**[7] (5.913−6.114 Å), and **CB**[8] (6.041−6.171 Å).[1,15] The distances between oxygen atoms of adjacent glycoluril rings (O6−O8 and O15−O17) are 3.405 and 3.309 Å (**30*C***) and 3.424 and 3.389 Å (**38*C***), respectively. These distances are larger than those observed in the crystal structures of Me_{10}**CB**[5] (average, 3.177 Å; range, 3.141−3.218 Å)[13] and **CB**[5] (average, 3.310 Å; range, 3.184−3.602 Å), comparable to those of **CB**[6] (average, 3.4025 Å; range, 3.138−3.624 Å), and shorter than those of **CB**[7] (average, 3.627 Å; range, 3.405−3.859 Å) and **CB**[8] (average, 3.810 Å; range, 3.695−3.906 Å).[1,15]

In constrast to **30*C*** and **38*C***, diastereomer **38*S*** crystallizes in an S-shaped conformation that displays two ethoxycarbonyl groups on each face of the molecule. One of the most interesting features of the crystal structure of **38*S*** is the close proximity of methylene carbon atom C6D to the centroid of the aromatic ring defined by C9A−C10−C11−C12−C13−C13A (3.713 Å). One of the protons attached to C6D is a mere 2.951 Å from the centroid of this aromatic ring. The close proximity of this proton to the center of the aromatic ring places it in its shielding region, which provides an explanation for the observation of the significant upfield shifts observed for these protons in the ^{1}H NMR of the S-shaped diastereomers. The most notable structural effect of the relative stereochemistry of the S-shaped diastereomers is present in the central eight-membered ring. For example, the sums of the bond angles around ureidyl nitrogen atoms N6, N7, N15, and N16 of **38*S*** amount to 350.1°, 357.9°, 359.9°, and 346.3°. N atoms N6 and N16 are decidedly nonplanar, suggesting the presence of strain relative to C-shaped diastereomers **30*C*** (average, 359.4°; range, 358.3°−359.9°) and **38*C*** (average, 359.5°; range, 359.0°−360°) and cucurbiturils Me_{10}**CB**[5] (average, 359.7°; range, 359.5°−360), **CB**[5] (average, 358.7°; range, 357.3°−359.9°), **CB**[6] (average, 358.8°; range, 356.0°−360°), **CB**[7] (average, 358.1°; range, 354.9°−359.9°), and **CB**[8] (average, 357.3°; range, 355.3°−358.2°).[1,13,15] Other structural features are comparable between the C- and S-shaped diastereomers. For example, the N6−C7−N7 and N15−C16−N16 bond angles measure 110.9° and 113.9°, values only slightly smaller than those observed for **30*C*** and **38*C***. The substituents on the convex face of the glycoluril rings are once again nearly eclipsed with C5C−C5B−C6B−C6C and C7C−C7B−C8B−C8C dihedral angles of −5.0° and −5.5°.

Homodimerization Reactions of Cyclic Ethers. The mechanistic rationale proposed in Scheme 2 suggests that cyclic ethers should also participate in this dimerization reaction (Scheme 4). Table 4 shows the results of the dimerization reactions from cyclic ethers that we have performed to date. Entries 1−6 illustrate the influence of the solubilizing groups on the convex face of the glycoluril skeleton on the dimerization reaction. Substrates **5a**, **e**, and **f** (entries 1, 5, and 6) that bear electron withdrawing carboxylic acid derivatives on their convex face are efficient substrates yielding only the C-shaped diastereomers in high yield. As in the case of the dimerization from the ureidyl NH compounds (Table 3), the substrates bearing Ph, fused-cyclohexyl, and 2-pyridyl substituents are poor substrates for the reaction (Table 4, entries 2−4), and both **5b** and **5d** lead to side products (±)-**35** and (±)-**36**. Compounds bearing functionalized *o*-xylylene rings are also acceptable substrates for this reaction (Table 4, entries 1, 7, and 8). Interestingly, we could not detect either **39*C*** or **39*S*** in the dimerization reaction with **27**. Similar behavior was observed in the dimerization reaction of **17** (Table 3, entry 6).

SCHEME 5. Dimerization Reactions from Ureidyl NH and Cyclic Ether Compounds



The survey of the substrates that participate effectively in this reaction is not as extensive as that described in Table 3 because the cyclic ethers themselves must be derived from the corresponding compounds containing ureidyl NH groups. Additionally, a comparison of the results obtained by these two methods (Table 3, entries 1−7 versus Table 4, entries 1−4 and 7−9) indicates that dimerization occurs in comparable yield in most cases. The single exception is the dimerization reaction of phenyl glycoluril (**5b**), a poor substrate for our reaction, which yields **30*C*** only from **4b** (Table 3, entry 2 versus Table 4, entry 2). These considerations suggest that the method described in Table 3 is preferable, since the cyclic ether substrates are themselves derived from the ureidyl NH compounds in only moderate yield (Chart 4, Table 2).

Heterodimerization Reactions of Ureidyl NH Compounds and Cyclic Ethers. The dimerization reactions described in Tables 3 and 4 offer two routes to the preparation of methylene-bridged glycoluril dimers. Of these two methods, the direct dimerization of the ureidyl NH compounds is preferable. On the basis of the mechanism of the dimerization reaction proposed in Scheme 2, we considered the possibility of performing a selective heterodimerization reaction by the reaction between 1 equiv of ureidyl NH compound and 1 equiv of cyclic ether (Scheme 5). The success of this method, the selective synthesis of a dimer comprising two different *o*-xylylene rings, requires a fast reaction between intermediates **45** and **51** (Scheme 2) and that the equilibria connecting those intermediates (via **46** and **47**) that result in the scrambling of the locations of the methylene bridges are slow relative to methylene-bridged glycoluril dimer formation.

Initially, we choose to study reactions between ureidyl NH compounds and cyclic ethers that would result in homodimeric species to limit the potential complexity of the reaction. Table 5 summarizes the results of the experiments that we performed. The effects of the solubilizing groups on the convex face of the glycoluril on the dimerization reaction (Table 5, entries 1−4) are similar to those observed for the direct dimerization of **4a**−**d** (Table 3) or **5a**−**d** (Table 4). Glycoluril derivatives bearing electron withdrawing ethoxycarbonyl groups (Table 5, entry 1) dimerized much more readily than those bearing phenyl or fused cyclohexyl groups (entries 2 and 4), and those bearing the readily protonated pyridyl substituents (entry 3) were resistant to dimerization. Those glycoluril derivatives bearing ethoxycarbonyl solubilizing groups that undergo smooth homodimerization also yield dimers by the heterodimerization route (Table 5, entries 5 and 7; Table 4, entries 7 and 8; Table 3, entries 5 and 7). There are situations, however, where the heterodimerization reaction is preferable to either of the two homodimerization pathways. For example, even though neither homodimerization pathway allowed the detection of either **39*C*** or **39*S*** (Table 3, entry 6; Table 4, entry 9), the heterodimerization pathway (Scheme 5) allowed the isolation of **39*C*** in good yield (Table 5, entry 6). In those cases, where direct dimerization reactions fail, the heterodimerization route offers a viable alternative.

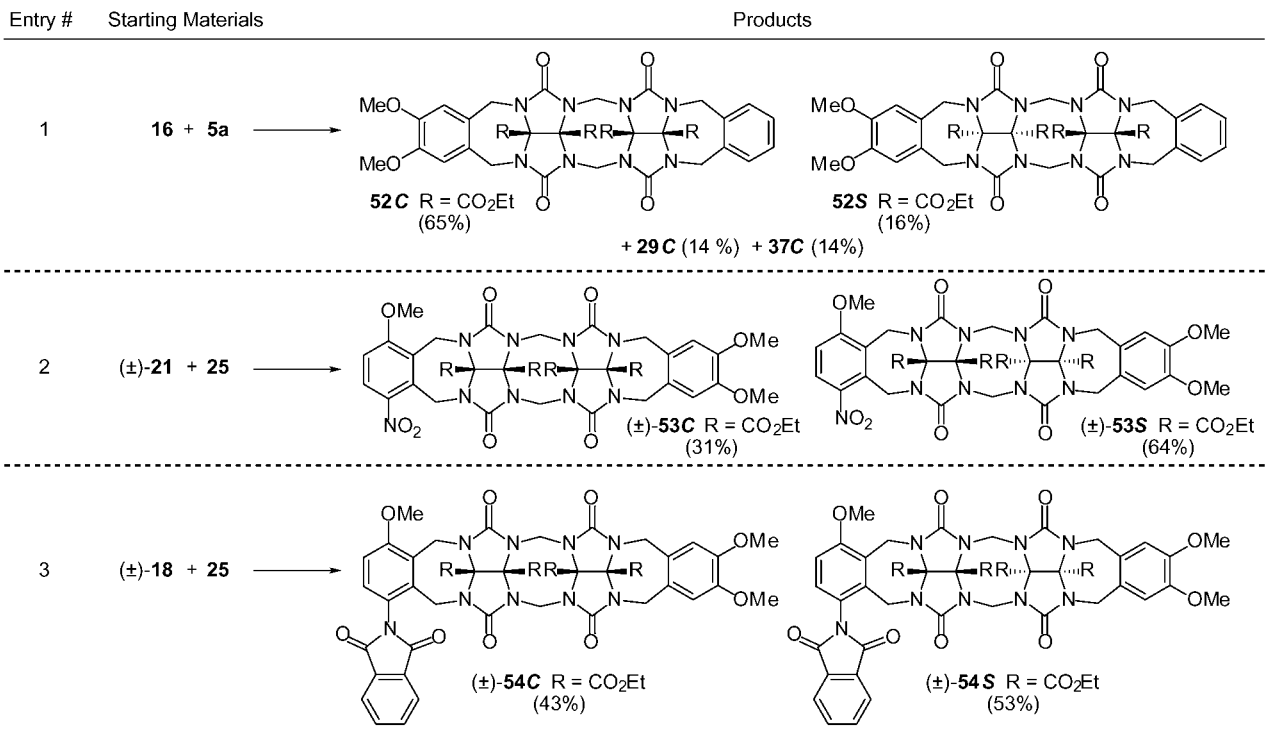
TABLE 5. Dimerization Reactions from Ureidyl NH and Cyclic Ether Compounds

entry	R	starting material	C-shaped (yield, %)	S-shaped (yield, %)	side product(s) (yield, %)
1	CO_2Et	**4a** + **5a**	**29*C*** (89)	**29*S*** (2)	
2	Ph	**4b** + **5b**	**30*C*** (16)	**30*S*** (nd)	**35b** (70)
3	2-pyridyl	**4c** + **5c**	**31*C*** (nd)[a]	**31*S*** (nd)	
4	$(CH_2)_4$	**4d** + **5d**	**32*C*** (30)	**32*S*** (nd)	**35d** (12), **36d** (10)
5	CO_2Et	**16** + **25**	**37*C*** (91)	**37*S*** (2)	
6	CO_2Et	**17** + **27**	**39*C*** (56)	**39*S*** (nd)	
7	CO_2Et	**19** + **26**	**38*C*** (90)	**38*S*** (3)	

[a] nd = not detected.

To fully demonstrate the synthetic utility of the heterodimerization reaction (Scheme 5), it was necessary to prepare true heterodimers, methylene-bridged glycoluril dimers comprising two different *o*-xylylene rings, and show that these heterodimers are produced selectively at the expense of the corresponding homodimers. Table 6 shows the results of three heterodimerization reactions that we have performed. Entry 1 shows the heterodimerization of dimethoxyxylylene ureidyl NH compound **16** and xylylene cyclic ether **5a**. In theory, six dimers might be formed (homodimers **29*C***, **29*S***, **37*C***, and **37*S*** and heterodimers **52*C*** and **52*S***); in practice, we isolate the two heterodimers and the two C-shaped homodimers. The desired heterodimers **52*C*** and **52*S*** were obtained in high combined yield (81%), with a modest level of diastereoselectivity favoring the C-shaped diastereomer **52*C***. This level of diastereoselectivity was particularly surprising, considering the fact that the relative stereochemistry of the product is set during the first covalent bond forming reaction between the two reaction partners (Scheme 2, (±)-**45** + (±)-**51**). In a separate report, we present a mechanistic rationale for the enhanced yield of the

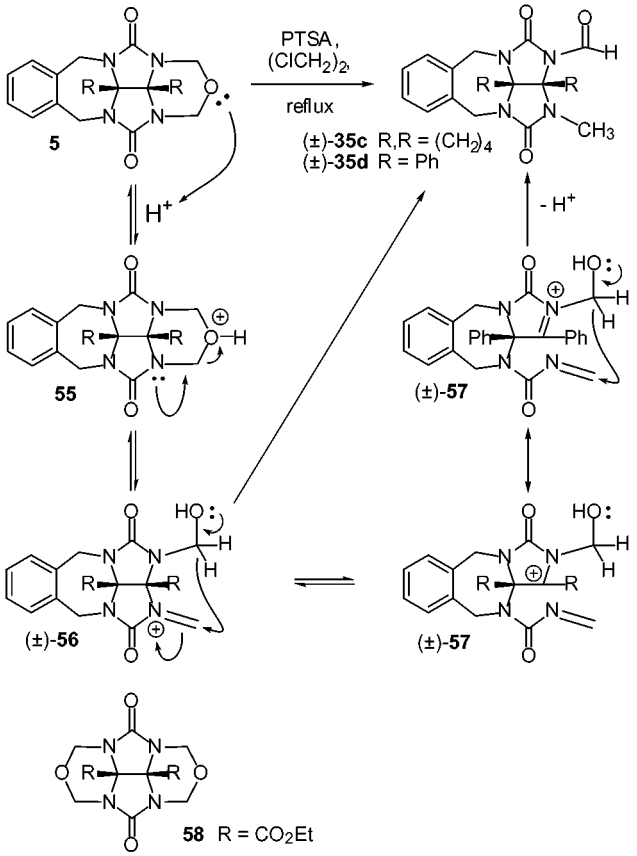
TABLE 6. Heterodimerization Reactions



C-shaped heterodimer.[54] Table 6 (entries 2 and 3) shows the reactions of the racemic ureidyl NH compounds (±)-**21** and (±)-**18** with the dimethoxyxylylene cyclic ether **25**. In these cases, of the six possible products, we observe only two, the desired heterodimers, and isolate them in excellent combined yield. In contrast to entry 1 (Table 6), these two heterodimerization reactions produce the S-shaped diastereomers with modest diastereoselectivities. These three experiments and the results of Tables 3−5 that demonstrate a preference for the C-shaped diastereomers suggest that the formation of the mixture of C- and S-shaped diastereomers occurs under kinetic control (Table 6, entries 2 and 3) and that the preference for the C-shaped heterodimer (Table 6, entry 1) reflects thermodynamic control.[54]

Substituent Effects on the Mechanism of the Dimerization Reaction and Implications for CB[*n*] Synthesis. To date, **CB**[*n*] and fully substituted derivatives have been synthesized using glycolurils **1d**−**f**.[1,4,13−17,21] These three glycoluril derivatives represent only one of the four main classes of commonly encountered glycolurils (alkyl, aromatic, heteroaromatic, and carboxylic acid derivative). We were surprised by the lack of success in the synthesis of **CB**[*n*] derivatives using other glycoluril derivatives. The formation of cyclohexyl- and phenyl-substituted dimers **32*C*** and **30*C***, in sharp contrast to the dimerization reactions involving ethoxycarbonyl-substituted glycolurils, proceeds in modest yields and with the formation of side products **35** and **36**. These side products provide clues for the lack of success in the synthesis of fully substituted **CB**[*n*] from **1b**. Scheme 6 shows a mechanistic proposal for the formation of side products (±)-**35**. This mechanistic proposal is illustrated

SCHEME 6. Proposed Mechanism for the Formation of (±)-35 in the Dimerization Reactions



for the dimerization reactions of cyclic ethers **5**, but the mechanisms of all three types of dimerization reactions potentially involve common intermediates (Scheme 2).

(54) Chakraborty, A.; Wu, A.; Witt, D.; Lagona, J.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2002**, *124*, 8297−8306.

Cyclic ether **5** undergoes protonation on its ether oxygen (**55**), followed by ring opening to yield iminium ion (±)-**56**. Formally, the conversion of (±)-**56** into the observed products (±)-**35** occurs by a hydride shift. Formulation of the reaction as a hydride shift from (±)-**56** ignores the fact that only phenyl and cyclohexyl glycolurils generate these side products, since one would also expect ethoxycarbonyl-substituted glycolurils to generate similar side products. We have never observed aldehydic side products in the dimerization of ethoxycarbonyl-substituted glycoluril derivatives. Alternatively, one can postulate the formation of intermediates (±)-**57**. One would expect that intermediates (±)-**57** would be favored when R,R = $(CH_2)_4$ and R = Ph because of the ability of these groups to stabilize adjacent carbocations but disfavored when R = CO_2Et, since this group would destabilize an adjacent positive charge. The conversion of (±)-**57** into (±)-**35** is then formulated as an ene reaction of a cationic *N*-acyl iminium ion with an imine.[55] The lower yield obtained in the synthesis of **30*C*** than in that of **32*C*** can be explained by the fact that the phenyl substituents are better able to stabilize the adjacent positive charge in (±)-**57**, thereby leading to the enhanced yield of (±)-**35b** compared to (±)-**35d**. These observations have implications for the synthesis of derivatives of **CB**[*n*]. They suggest that the **CB**[*n*] synthesis is likely to be most successful in the case of glycoluril derivatives bearing electron withdrawing substituents on their convex face and least successful in the case of electron donating substituents that are able to stabilize adjacent positive charges. The recent report of the synthesis of Cy_6**CB**[6] and Cy_5**CB**[5] in 2% and 16% yields, respectively, suggests that alkyl groups may be borderline substituents for the synthesis of **CB**[*n*].[21] However, if it is desired to use a glycoluril derivative containing electron donating groups on its convex face (e.g. **1b** or **d**) for **CB**[*n*] synthesis, then it would be prudent to perform such a reaction using heterodimerization conditions (Tables 5 and 6),[16,26] involving the reaction of **1b** or **d** with, for example, **58** which is not prone to form aldehydic side products.

Conclusions

The outstanding molecular recognition properties of cucurbituril, its homologues **CB**[*n*], and its derivatives (Me_{10}**CB**[5], Cy_5**CB**[5], Cy_6**CB**[6], and Ph_2**CB**[6]) have prompted several groups to broaden the scope and define the limitations of cucurbituril synthesis. We have taken a multistep synthetic organic approach based on the identification of methylene-bridged glycoluril dimers **2*C*** and **2*S*** as the fundamental building blocks in **CB**[*n*] synthesis. We examined condensation reactions between glycoluril derivatives bearing one *o*-xylylene wall and either free ureidyl NH groups (**4a**−**d** and **16**−**24**) or cyclic ether (**5a**−**f** and **25**−**27**) groups. Three different methods, the condensation reactions of **4a**−**d** and **16**−**24** with paraformaldehyde (Table 3), the homodimerization of cyclic ethers **5a**−**f** and **25**−**27** (Table 4), and the heterodimerization reactions (Tables 5 and 6) of cyclic ethers and ureidyl NH compounds, all deliver the C- and S-shaped diastereomers in good to excellent yields with glycoluril derivatives bearing electron withdrawing carboxylic acid derivatives on their convex face. The C-shaped compound is usually formed preferentially in diastereoselective reactions. Of these three synthetic methods, we prefer the direct dimerization reaction of the ureidyl NH compounds (Scheme 3, Table 3), since it produces the C- and S-shaped dimers in similar yields and diastereoselectivities to those of the dimerization of cyclic ethers (Scheme 4, Table 4) but involves fewer synthetic steps. The heterodimerization reactions (Tables 5 and 6) are most useful when it is necessary to access methylene-bridged glycoluril dimers bearing differentially substituted rings or when substrates undergo low yielding homodimerization reactions. Glycoluril derivatives bearing phenyl and fused cyclohexyl groups are poor substrates for the dimerization reactions because they are able to stabilize adjacent positive charges leading to aldehydic side products. The development of synthetic methods for the synthesis of methylene-bridged glycoluril dimers offers the opportunity to study the fundamental steps in **CB**[*n*] synthesis[54] and the potential to expand the range of **CB**[*n*] homologues and derivatives.

Experimental Section

General. Starting materials were purchased from commercial suppliers and were used without further purification. Compounds **5a**, **b**, **e**, and **f**, **25**, **27**, **29*C***, **33*C***, **34*C***, **37*C***, **37*S***, **39*C***, **52*C***, **52*S***,[28] **29*S***,[54] as well as **12**, (±)-**21**, (±)-**53*S***, and (±)-**53*C***[34] were prepared according to literature procedures. THF and toluene were distilled from sodium benzophenone ketyl, and methylene chloride was distilled from CaH_2 immediately before use. TLC analyses were performed using precoated glass plates from Analtech or E. Merck. Column chromatography was performed using silica gel (230−400 mesh, 0.040−0.063 μm) from E. Merck using eluents in the indicated v/v ratio. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on a spectrophotometer as KBr pellets or thin films on NaCl plates and are reported in inverse centimeters. NMR spectra were measured at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Fast atom bombardment (FAB) mass spectra were obtained using the indicated matrix. The matrix "magic bullet" is a 5:1 (w/w) mixture of dithiothreitol−dithioerythritol. Elemental analyses were performed by Midwest MicroLab (Indianapolis, IN).

Representative Experimental Procedure from Table 1 (19). Glycoluril **1a** (8.00 g, 28.0 mmol) was dissolved in anhyd DMSO (100 mL) under N_2, and *t*-BuOK (5.91 g, 52.7 mmol) was added. After stirring for 15 min, 1,2-bis(chloromethyl)-4,5-dimethylbenzene (1.26 g, 6.20 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 anhyd $MgSO_4$. After filtration and rotary evaporation, the residue was purified by flash chromatography (SiO_2, $CHCl_3$/MeOH 25:1) to give **19** (1.76 g, 4.22 mmol, 68%) as a white solid. Mp 236 °C. TLC ($CHCl_3$/MeOH, 25:1) R_f 0.23. IR (KBr, cm^{-1}): 3217 s, 3019 m, 2940 m, 1710 s, 1464 m, 1368 m, 1270 m, 1145 m, 1034 s. ^{1}H NMR (400 MHz, DMSO-d_6): 8.38 (s, 2H), 6.99 (s, 2H), 4.48 (d, J = 15.8, 2H), 4.32 (d, J = 15.8, 2H), 4.19 (q, J = 7.1, 2H), 4.09 (q, J = 7.1, 2H), 2.12 (s, 6H), 1.19 (t, J = 7.1, 3H), 1.16 (t, J = 7.1, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 167.0, 166.6, 157.5, 135.6, 135.0, 130.9, 82.9, 74.4, 63.1, 62.9, 43.9, 19.2, 14.2, 14.2. MS

(55) Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347−360. The conversion of (±)-**57d** into (±)-**35d** could also conceivably deliver the compound with the *trans*-fused glycoluril derivative, whereas this transformation would be precluded by the cyclohexyl ring of (±)-**35c**. In either case, the comparatively high energy *trans*-fused ring system has never, to the best of our knowledge, been observed in glycoluril derivatives.

(FAB, magic bullet): *m/z* 417 (100, $[M + H]^+$). HRMS (FAB, magic bullet): *m/z* 417.1774 ($[M + H]^+$, $C_{20}H_{25}N_4O_6$, calcd 417.1774). Anal. Calcd for $C_{20}H_{24}N_4O_6$ (416.17): C, 57.68; H, 5.81. Found: C, 57.66; H, 5.78.

Representative Procedure from Table 2 (5d). A mixture of **4d** (435 mg, 1.46 mmol) and paraformaldehyde (438 mg, 14.6 mmol) in TFA (5 mL) was stirred and heated at reflux for 20 h. After rotary evaporation, the residue was dissolved in EtOAc (150 mL), washed with saturated aq Na_2CO_3, dried over anhyd $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, $CHCl_3$/MeOH 50:1) to give **5d** (314 mg, 0.924 mmol, 63%) as a white solid. Mp 245−246 °C. TLC ($CHCl_3$/MeOH 50:1) R_f 0.33. IR (KBr, cm^{-1}): 2949 m, 2911 m, 2876 m, 1707 s, 1472 s, 1446 s, 1239 s, 1005 s, 740 s. ^1H NMR (400 MHz, $CDCl_3$): 7.40−7.35 (m, 2H), 7.25−7.20 (m, 2H), 5.30 (d, $J = 11.3$, 2H), 4.67 (d, $J = 15.8$, 2H), 4.54 (d, $J = 11.3$, 2H), 4.35 (d, $J = 15.8$, 2H), 2.19 (br m, 2H), 2.08 (br m, 2H), 1.66 (br m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 157.4, 136.9, 129.8, 128.1, 71.8, 70.9, 44.0, 25.3, 24.3, 14.9, 14.8. (12 resonances expected, 11 observed). MS (FAB, magic bullet): *m/z* 341 (100, $[M + H]^+$). HRMS (FAB, magic bullet): *m/z* 341.1626 ($[M + H]^+$, $C_{18}H_{21}N_4O_3$, calcd 341.1614).

Representative Procedure for Table 3 (38*C* and 38*S*). A mixture of PTSA (0.168 g, 0.884 mmol) and $ClCH_2CH_2Cl$ (10 mL) was heated under N_2 at reflux for 30 min under an addition funnel filled with molecular sieves (4 Å). Compound **19** (92.0 mg, 0.221 mmol) and paraformaldehyde (20.0 mg, 0.663 mmol) were added, and reflux was continued for 48 h. The reaction mixture was diluted with EtOAc (150 mL), washed with saturated Na_2CO_3, dried over anhyd $MgSO_4$, and concentrated. Flash chromatography (SiO_2, $CHCl_3$/CH_3CN 20:1) gave **38*C*** (67.0 mg, 0.0782 mmol, 75%) and **38*S*** (5.2 mg, 0.0061 mmol, 6%) as white solids. Compound **38*C***: mp > 300 °C. TLC ($CHCl_3$/CH_3CN 15:1) R_f 0.22. IR (KBr, cm^{-1}): 2965 w, 1747 s, 1456 m, 1256 m, 1021 m. ^1H NMR (400 MHz, $CDCl_3$): 6.99 (s, 4H), 6.02 (d, $J = 16.0$, 2H), 4.79 (d, $J = 16.0$, 4H), 4.58 (d, $J = 16.0$, 2H), 4.32 (d, $J = 16.0$, 4H), 4.17 (m, 8H), 2.12 (s, 12H), 1.29 (t, $J = 7.2$, 6H), 1.24 (t, $J = 7.2$, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 165.0, 154.6, 136.4, 133.5, 131.1, 80.1, 78.7, 63.7, 63.3, 47.8, 44.9, 19.2, 13.9, 13.9. MS (FAB, magic bullet): *m/z* 857 (27, $[M + H]^+$), 174 (100, $[C_{11}H_{12}NO]^+$). HRMS (FAB, magic bullet): *m/z* 857.3440 ($[M + H]^+$, $C_{42}H_{49}N_8O_{12}$, calcd 857.3470). X-ray crystal structure. Anal. Calcd for $C_{42}H_{48}N_8O_{12}$ (856.88): C, 58.87; H, 5.65. Found: C, 58.74; H, 5.60. Compound **38*S***: mp 297−299 °C. TLC ($CHCl_3$/CH_3CN 20:1) R_f 0.20. IR (KBr, cm^{-1}): 2980 w, 1766 s, 1742 s, 1720 s, 1456 s, 1424 m, 1387 s, 1308 m, 1250 m, 1157 m, 1020 m. ^1H NMR (400 MHz, $CDCl_3$): 7.07 (s, 4H), 5.00 (s, 4H), 4.74 (d, $J = 16.0$, 4H), 4.26 (d, $J = 16.0$, 4H), 4.19 (q, $J = 7.1$, 4H), 3.58 (q, $J = 7.1$, 4H), 2.16 (s, 12H), 1.25 (t, $J = 7.1$, 6H), 1.04 (t, $J = 7.1$, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.4, 164.2, 155.3, 136.4, 133.4, 131.1, 81.8, 78.5, 63.6, 51.8, 44.9, 19.1, 13.9, 13.6 (15 resonances expected, 14 observed). MS (FAB, magic bullet): *m/z* 857 (30, $[M + H]^+$), 174 (100, $[C_{11}H_{12}NO]^+$). HRMS (FAB, magic bullet): *m/z* 857.3490 ($[M + H]^+$, $C_{42}H_{49}N_8O_{12}$, calcd 857.3470). X-ray crystal structure. Anal. Calcd for $C_{42}H_{48}N_8O_{12}$ (856.88): C, 58.87; H, 5.65. Found: C, 58.69; H, 5.58.

Representative Procedure for Table 4 (32*C*, (±)-35d, and (±)-36d). A mixture of PTSA (760 mg, 4.00 mmol) and $ClCH_2CH_2Cl$ (5 mL) was heated at reflux for 30 min under an addition funnel filled with molecular sieves (4 Å). Compound **5d** (136 mg, 0.400 mmol) was added in one portion, and reflux was continued for 20 h. The reaction mixture was diluted with EtOAc (50 mL), washed with saturated aq Na_2CO_3, dried over anhyd $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, $CHCl_3$/MeOH 25:1) to yield **32*C*** (42.5 mg, 0.0685 mmol, 34%), (±)-**35d** (21.2 mg, 0.0624 mmol, 16%), and (±)-**36d** (14.8 mg, 0.0474 mmol, 12%) all as white solids. Compound **32*C***: mp 370 °C dec. TLC ($CHCl_3$/MeOH 25:1) R_f 0.09. IR (KBr, cm^{-1}): 2948 w, 2875 w, 1709 s, 1464 s, 1422 m, 1308 m, 1225 m, 759 m, 737 m. ^1H NMR (400 MHz, CF_3COOH, D_2O-cap.): 7.40−7.35 (br m, 8H), 6.00 (d, $J = 16.6$, 2H), 4.92 (d, $J = 16.2$, 4H), 4.73 (d, $J = 16.2$, 4H), 4.67 (d, $J = 16.6$, 2H), 2.60−2.50 (m, 8H), 2.00−1.85 (br m, 8H). ^{13}C NMR (100 MHz, CF_3COOH, D_2O-cap.): 160.8, 136.4, 131.5, 131.1, 82.4, 79.9, 46.3, 46.1, 26.0, 25.6, 16.5, 16.0. MS (FAB, magic bullet): *m/z* 621 (100, $[M + H]^+$). HRMS (FAB, magic bullet): *m/z* 621.2968 ($[M + H]^+$, $C_{34}H_{37}N_8O_4$, calcd 621.2938). Compound (±)-**35d**: mp 223−225 °C. TLC ($CHCl_3$/MeOH 50:1) R_f 0.37. IR (KBr, cm^{-1}): 2948 w, 2875 w, 1738 s, 1706 s, 1457 s, 1417 m, 1306 m, 758 m. ^1H NMR (400 MHz, $CDCl_3$): 8.93 (s, 1H), 7.40−7.30 (m, 2H), 7.30−7.20 (m, 2H), 4.79 (d, $J = 15.6$, 1H), 4.72 (d, $J = 15.8$, 1H), 4.41 (d, $J = 15.6$, 1H), 4.30 (d, $J = 15.8$, 1H), 2.86 (s, 3H), 2.50−2.20 (m, 3H), 2.10−2.00 (m, 1H), 1.70−1.50 (br m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.8, 156.8, 152.9, 136.8, 135.6, 130.0, 129.3, 128.5, 128.2, 76.8, 76.2, 43.6, 43.4, 27.4, 24.7, 23.9, 14.9, 14.5. MS (FAB, magic bullet): *m/z* 341 (60, $[M + H]^+$), 55 (100). HRMS (FAB, magic bullet): *m/z* 341.1601($[M + H]^+$, $C_{18}H_{21}N_4O_3$, calcd 341.1614). Compound (±)-**36d**: mp 314 °C dec. TLC ($CHCl_3$/MeOH 25:1) R_f 0.27. IR (KBr, cm^{-1}): 3219 m, 2948 m, 1718 s, 1697 s, 1483 s, 1416 m, 764 m. ^1H NMR (400 MHz, $CDCl_3$): 7.35−7.10 (m, 4H), 6.06 (br s, 1H), 4.66 (d, $J = 15.7$, 1H), 4.64 (d, $J = 15.7$, 1H), 4.30 (d, $J = 15.7$, 1H), 4.28 (d, $J = 15.7$, 1H), 2.59 (s, 3H), 2.25−2.15 (m, 1H), 2.10−1.70 (m, 3H), 1.70−1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.2, 157.4, 137.3, 136.9, 129.8, 129.2, 127.9, 127.8, 77.5, 74.1, 43.6, 43.1, 27.9, 26.0, 24.5, 16.5, 16.2. MS (FAB, magic bullet): *m/z* 313 (100, $[M + H]^+$). HRMS (FAB, magic bullet): *m/z* 313.1660 ($[M + H]^+$, $C_{17}H_{21}N_4O_2$, calcd 313.1664).

Representative Procedure for Table 5 (30*C* and (±)-35b). A mixture of PTSA (5.000 g, 26.3 mmol) in $ClCH_2CH_2Cl$ (25 mL) was heated at reflux for 30 min under an addition funnel filled with molecular sieves (4 Å). Compounds **4b** (1.042 g, 2.63 mmol) and **5b** (922.7 mg, 2.11 mmol) were added, and reflux was continued for 5 days. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated aq Na_2CO_3, dried over anhyd $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, $CHCl_3$/MeOH 50:1) to yield **30*C*** (282.7 mg, 0.35 mmol, 16%) and (±)-**35b** (642 mg, 1.47 mmol, 70%) as white solids. Compound **30*C***: mp 384 °C dec. TLC ($CHCl_3$/hexanes/EtOAc/MeOH 25:10:2:1) R_f 0.16. IR (KBr, cm^{-1}): 3062 w, 3034 w, 2962 w, 1734 s, 1450 s, 1426 m, 1286 m, 753 m, 697 m. ^1H NMR (400 MHz, $CDCl_3$): 7.40−7.30 (m, 8H), 7.10−6.95 (m, 6H), 6.95−6.80 (m, 10H), 6.55−6.50 (m, 4H), 5.89 (d, $J = 15.4$, 2H), 4.70 (d, $J = 15.5$, 4H), 4.03 (d, $J = 15.5$, 4H), 3.76 (d, $J = 15.4$, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 156.5, 136.4, 133.4, 132.0, 129.7, 128.8, 128.6, 128.4, 127.8, 127.6, 127.6, 86.1, 84.0, 47.7, 45.0 (16 resonances expected, 15 observed). MS (FAB, magic bullet): *m/z* 817 (30, $[M + H]^+$), 91 (100, $C_7H_7^+$). HRMS (FAB, magic bullet): *m/z* 817.3226 ($[M + H]^+$, $C_{50}H_{41}N_8O_4$, calcd 817.3251). Compound (±)-**35b**: mp 310−312 °C dec. TLC (hexanes/EtOAc 4:1) R_f 0.23. IR (KBr, cm^{-1}): 3061 w, 3024 w, 2925 w, 1746 s, 1711 s, 1461 m, 1450 m, 1303 m, 1285 m. ^1H NMR (400 MHz, $CDCl_3$): 9.19 (s, 1H), 7.40−6.90 (m, 13H), 6.75−6.60 (m, 1H), 4.95 (d, $J = 15.6$, 1H), 4.86 (d, $J = 15.6$, 1H), 4.29 (d, $J = 15.6$, 1H), 4.18 (d, $J = 15.6$, 1H), 2.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 160.3, 157.8, 154.2, 136.6, 135.3, 132.6, 131.4, 130.0, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 127.6, 127.5, 126.6, 85.9, 84.3, 45.3, 45.2, 29.5. MS (FAB, magic bullet): *m/z* 439 (72, $[M + H]^+$), 91 (100, $C_7H_7^+$). HRMS (FAB, magic bullet): *m/z* 439.1812 ($[M + H]^+$, $C_{26}H_{23}N_4O_3$, calcd 439.1770).

Representative Procedure for Table 6 ((±)-54*C* and (±)-54*S*). A mixture of PTSA (0.410 g, 2.15 mmol) in $ClCH_2CH_2Cl$ (20 mL) was heated under N_2 at reflux for 30 min under an addition funnel filled with molecular sieves (4 Å). Compound **25** (0.210 g, 0.43 mmol) and (±)-**21** (0.240 g, 0.43 mmol) were added, and heating was continued for 24 h. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated Na_2CO_3, dried over anhyd $MgSO_4$, and concentrated. Flash chromatography (SiO_2, $CHCl_3$/ CH_3CN 4:1) gave (±)-

54*S* (0.24 g, 0.23 mmol, 53%) and (±)-**54*C*** (0.19 g, 0.19 mmol, 43%). Compound (±)-**54*S***: mp > 330 °C dec. TLC ($CHCl_3/CH_3CN$ 4:1) R_f 0.40. IR (KBr, cm^{-1}): 2983 w, 2936 w, 2835 w, 1717 s, 1452 s, 1390 s, 1270 s. ^1H NMR (400 MHz, $CDCl_3$): 8.00−7.95 (m, 1H), 7.90−7.80 (m, 1H), 7.80−7.70 (m, 2H), 7.13 (d, J = 8.8, 1H), 6.96 (d, J = 8.8, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 5.75 (d, J = 16.2, 1H), 5.16 (d, J = 13.6, 1H), 5.07 (d, J = 13.6, 1H), 4.97 (d, J = 13.6, 1H), 4.75−4.60 (m, 4H), 4.34 (d, J = 16.2, 1H), 4.30−4.00 (m, 6H), 3.95−3.85 (m, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.60−3.50 (m, 1H), 3.40−3.30 (m, 1H), 1.30−1.00 (m, 9H), 0.96 (t, J = 7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.0, 167.0, 165.2, 165.1, 164.0, 163.9, 157.4, 155.3, 155.1, 154.8, 147.8, 136.3, 134.5, 134.3, 131.9, 131.3, 129.2, 128.6, 126.2, 124.1, 123.6, 122.5, 113.0, 112.9, 111.8, 81.6, 81.0, 78.8, 78.2, 64.1, 63.6, 63.4, 56.4, 55.9, 51.8, 44.7, 39.6, 36.3, 13.8, 13.6, 13.5, 13.4 (49 resonances expected, 42 observed). MS (FAB, magic bullet): m/z 1036 (100, $[M + H]^+$). HRMS (FAB, magic bullet): m/z 1036.3284 ($[M + H]^+$, $C_{49}H_{50}N_9O_{17}$, calcd 1036.3325). Compound (±)-**54*C***: mp > 330 °C dec. TLC ($CHCl_3/CH_3CN$ 4:1) R_f 0.19. IR (KBr, cm^{-1}): 2975 w, 2940 w, 2839 w, 174e, 1717 s, 1456 s, 1270 s, 1014 m, 909 m. ^1H NMR (400 MHz, $CDCl_3$): 7.95−7.90 (m, 1H), 7.85−7.80 (m, 1H), 7.70−7.60 (m, 2H), 7.13 (d, J = 8.8, 1H), 6.88 (d, J = 8.8, 1H), 6.74 (s, 1H), 6.71 (s, 1H), 6.05 (d, J = 16.0, 1H), 5.92 (d, J = 16.0, 1H), 5.62 (d, J = 16.0, 1H), 4.78 (d, J = 16.0, 1H), 4.73 (d, J = 16.5, 1H), 4.72 (d, J = 16.0, 1H), 4.64 (d, J = 16.0, 1H), 4.48 (d, J = 16.0, 1H), 4.34 (d, J = 16.0, 1H), 4.33 (d, J = 16.0, 1H), 4.25 (d, J = 16.5, 1H), 4.25−4.00 (m, 9H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 1.30−1.10 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.8, 166.5, 165.5, 165.4, 164.7, 164.6, 157.0, 154.5, 154.4, 154.4, 154.2, 147.6, 147.5, 135.7, 134.1, 134.0, 131.5, 131.1, 129.2, 128.3, 128.2, 125.3, 123.9, 123.3, 122.1, 112.7, 112.6, 111.4, 79.9, 79.5, 78.6, 63.5, 63.3, 63.2, 56.1, 55.6, 55.5, 47.7, 47.5, 44.8, 39.8, 36.4, 13.7, 13.7, 13.6, 13.6 (49 resonances expected, 46 observed). MS (FAB, magic bullet): m/z 1036 (100, $[M + H]^+$). HRMS (FAB, magic bullet): m/z 1036.3359 ($[M + H]^+$, $C_{49}H_{50}N_9O_{17}$, calcd 1036.3325).

X-ray Crystal Structures for 30*C*, 38*C*, and 38*S*. Detailed descriptions of the data collection, solution, and refinement of the structures can be found in the Supporting Information. Crystal data for **30*C***: $[C_{50}H_{40}N_8O_4][CHCl_3][C_7H_8]_2$ (1120.54); triclinic, space group $P1$; colorless block, a = 14.4877(12) Å, b = 14.8574(12) Å, c = 15.1182(12) Å; V = 2787.7(4) Å^3; Z = 2; T = 193(2) K; $R(F)$ = 0.0654; GOF on F^2 = 1.082. Crystal data for **38*C***: $[C_{42}H_{48}N_8O_{12}][NCCH_3]_2$ (938.99); orthorhombic, space group $Pna2_1$; colorless block, a = 10.7933(9) Å, b = 26.350(2) Å, c = 16.7931(14) Å; V = 4776.1(7) Å^3; Z = 4; T = 193(2) K; $R(F)$ = 0.0586; GOF on F^2 = 1.065. Crystal data for **38*S***: $[C_{42}H_{48}N_8O_{12}]$ (856.88); monoclinic, space group $P2_1/c$; colorless block, a = 20.9952(17) Å, b = 16.8963(13) Å, c = 11.9470(9) Å; V = 4083.8(6) Å^3; Z = 4; T = 193(2) K; $R(F)$ = 0.0774; GOF on F^2 = 1.087.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds and details of the X-ray crystal structures of **30*C***, **38*C***, and **38*S***. This material is available free of charge via the Internet at http://pubs.acs.org.

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