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The Synthetic Challenge of Thioglycolurils

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The very high stability of cucurbiturils under harsh acidic conditions and their reported prolific chemistry over more than three decades pose a question: why has no thiocucurbituril been reported to date? Furthermore, although glycoluril is a highly stable, easily accessible precursor of all cucurbiturils, its sulfur analog represents a yet unmet synthetic challenge. The reaction between glyoxal and thiourea was found to stop at the level of dihydroxyimidazolidine-2-thione, which is quite unstable under various acidic conditions. In an attempt to answer these questions, several stable analogs of thioglycoluril, that is, monothioglycoluril, ditolylthioglycoluril, and its diether derivative were prepared and characterized in the hope that they could be employed as building blocks for the synthesis of thiocucurbiturils. Several side products were also obtained that highlight the complex reactivity of thiourea in these reactions. The crystal structures of the above-mentioned thioglycolurils are dominated by networks of hydrogen-bonding interactions. Attempts to co-oligomerize these compounds with formaldehyde clearly suggest that it is impossible to synthesize thiocucurbiturils by the methods commonly used for the preparation of cucurbiturils. Given that thiocucurbiturils are expected to be stable molecules, alternative synthetic strategies that are different from the thermodynamically controlled approaches must be designed.

Introduction

Cucurbiturils have been attracting increasing attention because these exceptional host molecules exhibit useful binding properties and unique structures.[1] Their rich supramolecular chemistry and specific binding interactions to various organic guests and metal ions have led to a broad variety of applications, including chemical sensing, catalysis, and the ability to function as essential components of molecular architectures.[2] On these grounds, it is quite surprising that no attempt to prepare thiocucurbiturils has been reported within more than three decades of intense research on the chemistry of cucurbiturils. The incorporation of sulfur atoms within the framework of other macrocyclic host molecules has been quite rewarding. For example, thiacrown ethers exhibit moderate π acidity that has allowed them to coordinate transition-metal ions of low oxidation states.[3,4] Thiacalixarenes in which the methylene bridge of calixarenes is replaced by a sulfur atom or sulfoxide and sulfone derivatives can function as useful ion sensors.[5] Calixarenes bearing thiophenols rather than phenols offer unique conformational preferences and specific binding to metal ions.[6] Cyclodextrins with thiols at the 6-position form self-assembled monolayers on gold surfaces for various electrochemical applications.[7]

Aside from theoretical studies by Pichierri,[8,9] which predicted interesting ligation to metal ions and metal surfaces, there has been only circumstantial evidence on attempts to prepare thiocucurbiturils. For example, shortly after his discovery of the cucurbituril structure, Mock reported the preparation of monothioglycoluril.[10] Other attempts to prepare thioglycolurils probably reflect similar intentions.[11]

This situation suggests that although thiocucurbiturils are expected to be thermodynamically stable, their synthesis represents a significant challenge. Herein, we address this problem and delineate the reasons why it is difficult to synthesize thiocucurbiturils by using the same chemistry that has proven so useful for the preparation of cucurbiturils (Scheme 1).

Results and Discussion

Considering potential synthetic approaches to thiocucurbiturils, one could contemplate either direct thionation of cucurbiturils or acid-catalyzed condensation of thioglycolu-

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[‡] This article is dedicated to Dr. Mark Botoshansky, a devoted unabated crystallographer, whose life came to an abrupt end by an incurable illness shortly before the manuscript was submitted.

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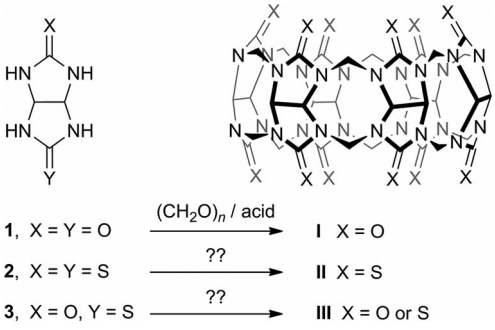
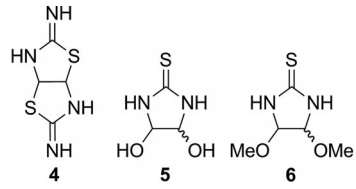


Scheme 1. General synthesis of cucurbiturils and their sulfur analogs. The hexameric CB[6] represents the entire family of CB[*n*] = cucurbit[*n*]uril.

ril **2** or **3** with paraformaldehyde (Scheme 1). Although the first approach seems quite attractive, it seems to be impractical because of the insolubility of cucurbiturils in organic solvents that are essential for reactions with a phosphetane agent (Lawesson's reagent).[12] Furthermore, it has already been reported that direct thionation of urea derivatives, including glycolurils, can work only if all of the nitrogen atoms are fully substituted. Otherwise, the reaction proceeds through C–N bond cleavage to produce isothiocyanates or aminoisothiocyanates.[13,14] Indeed, these findings were confirmed by our preliminary attempts.

The alternative approach, which is based on the classical employment of glycolurils, depends on the accessibility, stability, and reactivity of **2** and **3**. Whereas the condensation reaction of urea with α-dicarbonyl compounds proceeds quantitatively, the analogous reaction with thiourea is not trivial. For example, the reaction between thiourea and glyoxal in aqueous HCl at 75 °C leads to a complex mixture of products, including 1,4-diaza-3,6-dithiabicyclo[3.3.0]octane-2,5-diimine (**4**),[15,16] thiohydantoin,[17] urea, 2-thioimidazole, and elemental sulfur (Table 1, entry 6). The reported formation of **2** under these conditions was found to be incorrect.[18] Yet, one analog of **2**, that is, cyclohexanothioglycoluril, was obtained in 26% yield from cyclohexane-1,2-dione and thiourea under milder acidic conditions, such as trifluoroacetic acid in toluene.[11]

We investigated the reaction between thiourea and glyoxal under milder conditions (Table 1), including ultrasonic irradiation, which was proven useful for the synthesis of glycoluril and hydantoin derivatives.[19] As can be seen from Table 1, **5** was formed exclusively as a *cis*/*trans* mixture with no evidence for the formation of **2**. Although only *trans*-**5** was previously characterized,[20] we identified both *cis*-**5** and *trans*-**5** and determined their ratio by ^{1}H NMR spectroscopy ([D$_6$]DMSO) on the basis of their resonances: δ= 8.56/8.83 (NH), 5.81/6.26 (OH), 5.03/4.73 ppm (CH), respectively. The corresponding ^{13}C NMR spectrum exhibited the *cis*/*trans* isomers at δ = 181.6/182.3, 80.0/87.4 ppm, respectively, in agreement with the generally observed spectral manifestation of internal *gauche* and *anti* O–C–C–O arrangements.[21]



Given that 4,5-dihydroxyimidazolidone, the oxygen analog of **5**, is a known intermediate in the synthesis of **1** from glyoxal and urea,[22] we attempted to prepare **2** by treating **5** with thiourea in aqueous hydrochloric acid. However, all reactions of **5** with either thiourea or urea at various pH values and different reaction times and temperatures resulted in the above-described product mixture that was usually obtained under harsh acidic conditions. These observations, as well as previous reports on the reactions of thiourea and benzil,[23] indicate that **5** is not a suitable precursor of **2**.

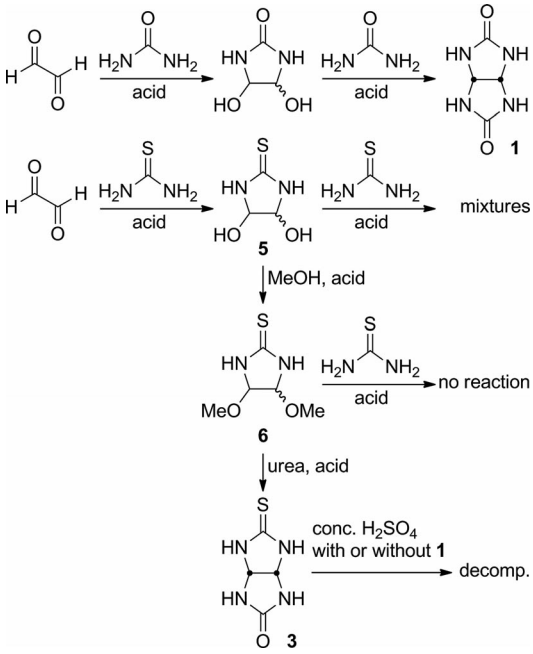
In an attempt to control the reactivity of **5**, we converted it into corresponding diether **6**.[24] Thus, **5** was treated with slightly acidic methanol to form *trans*-**6** in the form of a single stereoisomer (Scheme 2), as was evident by both ^{1}H NMR and ^{13}C NMR spectroscopy. All attempts to react **6** with thiourea under aqueous acidic conditions resulted in the same mixture that was obtained from **5** under these conditions. Nevertheless, partial success was achieved in the reaction of **6** with urea instead of thiourea, which led to monothioglycoluril, **3** in 45% yield[25] along with <5% of glycoluril (**1**, Table 2).

The observed acid-catalyzed conversion of **6** into glycolurils **3** and **1** at a ratio of 10:1 reflects a multistep mechanism with a series of protonation/deprotonation of heteroatoms, departure of various leaving groups, formation of heteroatom-stabilized carbocations, and nucleophilic attacks on these intermediates.[26,27] Given that all of these reactions are reversible, one would assume that the product distribution reflects thermodynamic control. However, the fact that **1**, **3**, and **6** have limited solubility in acidic water leads to the consequence that the reaction is, at least partially, kinetically controlled. Considering the pK_a values of

Table 1. Reaction between thiourea and glyoxal; all reactions were performed for 2 h.

Entry	Solvent	*T* [°C]	Thiourea/glyoxal	Catalyst	Yield [%] of **5** (*cis*/*trans*)[a]
1[b]	EtOH	55	2:1	KOH (2 equiv.)	>95 (15:85)
2[b]	EtOH	r.t.	2:1	NaOH (0.5 equiv.)	65 (10:90)
3[b]	EtOH/H_2O	55	2:1	acetic acid (pH 4)	>95 (15:85)
4	Water	65	2:1	none	90 (35:65)
5	Water	r.t.	2:1	none	85 (5:95)
6	Water	80	2–6:1	HCl (0.5–8 M)	trace

[a] Yield of isolated product. [b] Under ultrasonic irradiation (40 kHz).



Scheme 2.

Table 2. Reaction of **6** with urea under aqueous HCl (0.3 %) conditions at 80 °C.

Entry	**6**/urea	Time [h]	Yield [%] **3**[a]	**1**[b]
1	1:1	2	10	1
2	1:1.2	2	45	4.5
3	1:1.2	5	30	3
4	1:2	2	40	4
5	1:10	2	40	4

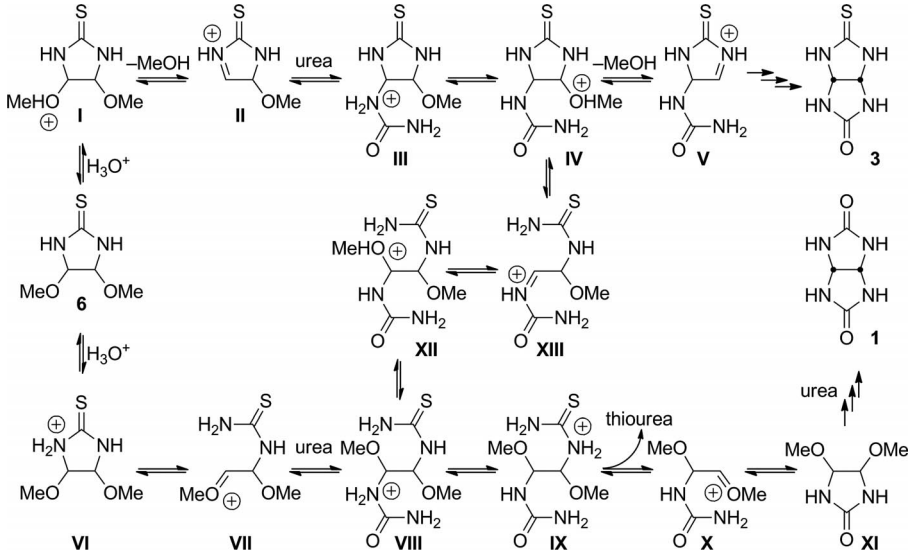
[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy.

the reagents involved in this reaction, their expected order of nucleophilicity would be: methanol > urea > thiourea. Accordingly, the order of their performance as a good leaving group upon protonation would be thiourea > urea > methanol. For example, intermediate **VIII** is expected to be more stable than intermediate **IX**, which implies that **IX** is more reactive than **VIII** (Scheme 3).

Thus, **6** is susceptible to protonation on either the methoxy group or the thiourea fragment to produce intermediate **I** or **VI**, respectively (Scheme 3). Departure of methanol from **I** and attack by urea on the resultant iminium cation would lead to intermediates **II** and **III**. The latter can undergo reversible proton transfer to form **IV**, which upon loss of a second molecule of methanol will produce **V**, a clear precursor of **3**. Similarly, intermediate **VI** could undergo a similar sequence of transformations along intermediates **VIII**–**X**, all the way to **XI**. The latter is a known intermediate on the way to glycoluril (**1**).[15] Clearly, various other steps are expected to occur under aqueous acidic conditions, such as the crossover between the upper and lower pathways in Scheme 3 by the interconversion of intermediates **VIII** and **IV** through intermediates **XII** and **XIII**.

The crystal structure of monothioglycoluril **3** (Figure 1) shows that both rings are nearly planar and that they adopt an envelope conformation with both the C=S and C=O groups at the flap position. The crystallographic unit cell belongs to the monoclinic crystal system with the non-centrosymmetric space group $P2_1$ and a single molecule in the asymmetric unit. The crystal data and structural refinement results are summarized in Table 3.

Notably, there is a 50:50 occupancy of oxygen and sulfur in each of the carbonyl/thiocarbonyl sites, and each molecule exhibits short contacts to the neighboring molecules. The crystal structure features chains of molecules along the *b* axis within the *bc* plane, and in each chain, the molecules present their convex face either up or down to form an anti-



Scheme 3. Protonation of the urea or thiourea fragment could occur on either nitrogen atom, as shown, for example, in intermediate **III** or **VI**, or on their O/S atoms.

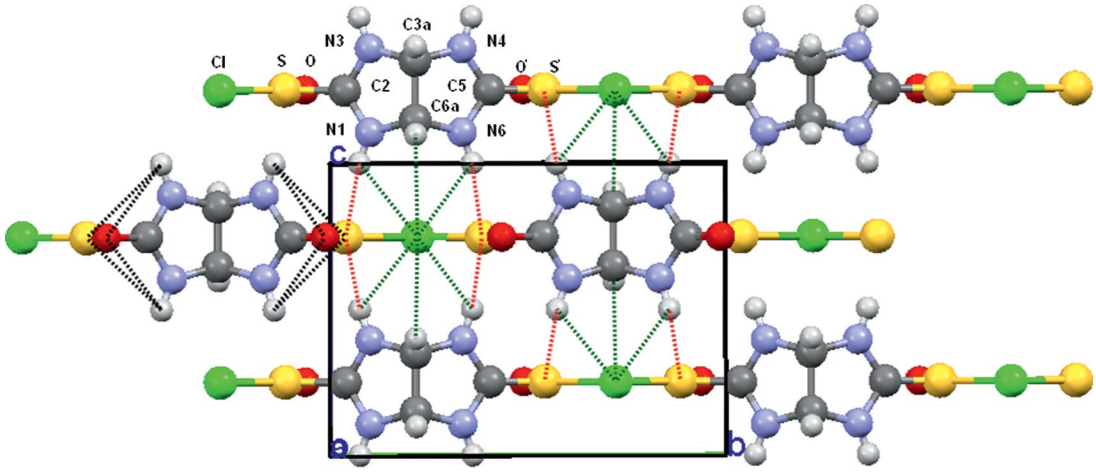


Figure 1. Crystal structure of **3** showing a layer of antiparallel molecular chains in the *bc* plane with intermolecular NH···S hydrogen bonds (red dashed lines), NH···Cl and CH···Cl hydrogen bonds (green dashed lines), and intramolecular C=S···HN and C=O···HN hydrogen bonds (black dashed lines). The atomic numbering refers to the symmetry operation [*x*, *y*, *z* + 1]. Color code: C, gray; N, blue; O, red; S, yellow; Cl, green; H, grayish.

Table 3. Crystallographic data and refinement details of **3**, **8**, and **10**.

	3	**8**	**10**
Formula	$C_4H_6N_4SOCl$	$C_{18}H_{18}N_4S_2{\cdot}2CH_4N_2S$	$C_{22}H_{22}N_4O_2S_2$
Formula weight	193.6	506.77	438.58
Density [g cm^{-3}]	2.344	1.305	1.371
T [K]	293(2)	293(2)	293(2)
Diffractometer	APEX2 DUO	KappaCCD	APEX2 DUO
Scan mode	ω scans	ω and ϕ scans	ω scans
Crystal size [mm]	0.26 × 0.20 × 0.16	0.28 × 0.15 × 0.10	0.44 × 0.26 × 0.19
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	$P2_1$	*Pnma*	$P2_1/n$
a [Å]	4.188(6)	9.289(2)	8.638(3)
b [Å]	10.252(2)	16.465(3)	11.375(4)
c [Å]	7.561(6)	16.864(3)	21.757(7)
α [°]	90	90	90
β [°]	90.37(4)	90	96.27(1)
γ [°]	90	90	90
V [Å^3]	324.6(5)	2579.2(9)	2125.0(13)
Z	2	4	4
F(000)	232	1064	920
θ max [°]	24.97	25.04	25.24
Unique reflections	673	2346	3765
$I > 2\sigma(I)$	575	1354	3351
R factor (all data)	0.0802	0.099	0.1165
R factor [$I > 2\sigma(I)$]	0.0752	0.051	0.0442
S	1.062	0.816	1.008

parallel array of alternating chains. Apparently, the main driving force for the formation of the antiparallel array of chains along the *b* axis is the complex network of hydrogen bonds, including NH···X (X = O/S), NH···Cl, and CH···Cl, all along the *a* axis. Remarkably, each chloride ion is engaged in six strong hydrogen bonds, all of which range between 2.65 and 2.80 Å. Every two molecules in the chain are connected by a chloride ion through their oxygen/sulfur atoms. Although the structure does not allow for specific assignment of either oxygen or sulfur on each site, the connecting chloride atom is asymmetrically positioned between these two heteroatoms at a short distance (2.26 or 2.08 Å) and a long distance (2.83 or 2.96 Å). These unprecedented contacts between a chloride ion and a carbonyl/thiocarbonyl have not yet been reported in the Cambridge Crystallographic Data Centre (CCDC). This unusual phenomenon, as well as the observed, relatively short carbonyl and thiocarbonyl bonds (1.25/1.46 and 1.49/1.63 Å, respectively) are currently under investigation in our laboratories.

Unfortunately, although **3** was now readily available in our hands, all attempts to employ it for the synthesis of thiocucurbiturils (Scheme 1) failed. Under the classical con-

ditions of cucurbituril synthesis, this compound decomposed to produce the above-mentioned mixture observed upon treatment of either **5** or **6** with strong acids.

Considering the limited stability of **2** and **3** under mildly acidic conditions, we turned our attention to disubstituted thioglycolurils, because these compounds can be produced under basic conditions from the corresponding benzil derivatives.[27] Thus, reaction of thiourea with 4,4′-dimethylbenzil at various molar proportions in basic ethanol afforded **7** along with ditolyl thioglycoluril (**8**; Table 4, entries 1–4). Remarkably, as long as the reaction and its workup were performed under basic conditions, the corresponding hydantoin **9** (Scheme 4) was not formed.[28] Furthermore, our observation that the ratio between **7** and **8** in the product mixture was independent of the ratio between the two reactants indicates that under the reaction conditions **7** is not a precursor of **8**.[27] Nevertheless, the product ratio was found to be dependent on the solvent. For example, whereas **7**/**8** = 40:60 in ethanol, by performing the reaction in either isopropanol or *tert*-butyl alcohol, the ratio changed to 25:75 or 12:88, respectively, with negligible changes in the overall yields. In contrast, by using polar solvents (Table 4, entries 7 and 8), the ratio was reversed to 85:15 in DMSO and to 93:7 in water.

Table 4. Reaction of thiourea with 4,4′-dimethylbenzil. All reactions were performed under basic conditions (KOH, 0.6 equiv.) by using ultrasonic irradiation (40 kHz, 55 °C, 2 h).

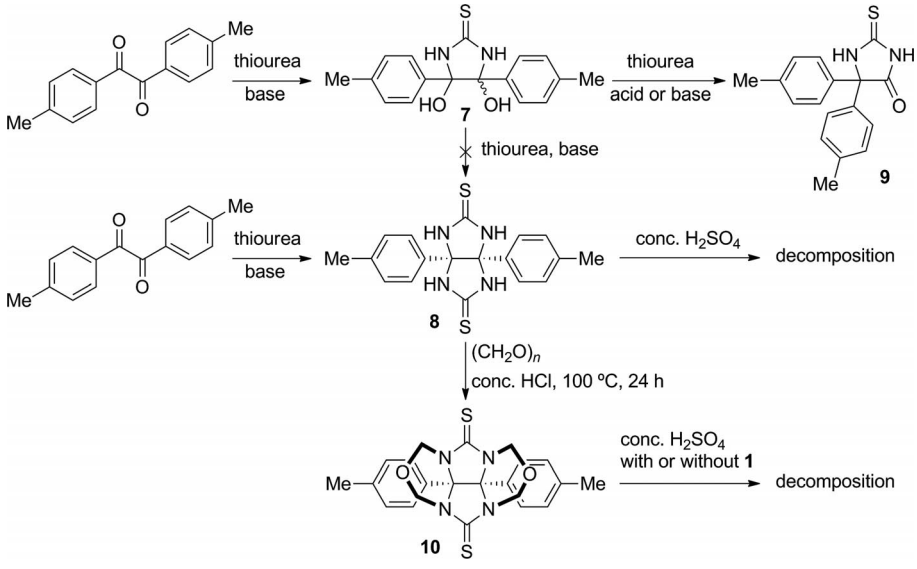
Entry	Solvent	Thiourea/4,4′-dimethylbenzil	Yield[a] [%] **7**	**8**
1	ethanol	1:1	50	25
2	ethanol	2:1	40	40
3	ethanol	3:1	40	57
4	ethanol	4:1	40	57
5	*i*PrOH	4:1	25	72
6	*t*BuOH	4:1	11	78
7	water	4:1	27	2
8[b]	DMSO	4:1	66	12

[a] Yield of isolated product. [b] Determined by analysis of the crude material by ^{1}H NMR spectroscopy.

Ditolyl thioglycoluril (**8**), which precipitated from the reaction mixture together with thiourea, was recrystallized from ethanol to give co-crystals of **8** and thiourea in a 1:2 ratio. As observed with **3**, the structure of **8** (Figure 2) shows that the two five-membered rings assume an envelope conformation in which both thiocarbonyl groups adopt the flap position. The crystallographic unit cell belongs to the orthorhombic crystal system with a space group *Pnma* showing half a molecule in the asymmetric unit. The crystal data and structural refinement results are summarized in Table 3. Expectedly, the aryl groups exhibit face-to-face stacking interactions with an angle of 40° between the two aromatic planes (Figure 2, left). Interestingly, this angle is smaller than the corresponding angle of 48°, which was observed for diphenyl thioglycoluril.[29] The crystal packing is dominated by a network of hydrogen-bonding interactions (Figure 2, right), which generally characterize crystal structures of thiourea derivatives.[30] Interestingly, the nitrogen atoms of both thiourea molecules function as both hydrogen-bond donors, NH···S, and hydrogen-bond acceptors, N···HC, with short contacts (2.82 Å) between the nitrogen atoms and the aromatic hydrogen atoms of **8**.

Substituted thioglycoluril **8** was found to be much more stable than **3** under acidic conditions. For example, **8** survived in concentrated H_2SO_4 at 90 °C for 4 h and at room temperature for 24 h. Nevertheless, no cyclic or acyclic co-oligomers could be observed in the reaction of **8** with formaldehyde under these conditions. Switching from sulfuric acid to concentrated HCl afforded diether derivative **10** in 82% yield (Scheme 4).

Compound **10**, which was crystallized from chloroform (Figure 3 and Table 3), shows that the two five-membered rings assume a half-chair conformation. Thus, the two bridge carbon atoms are significantly withdrawn from the plane defined by the remaining three ring atoms; the tor-



Scheme 4.

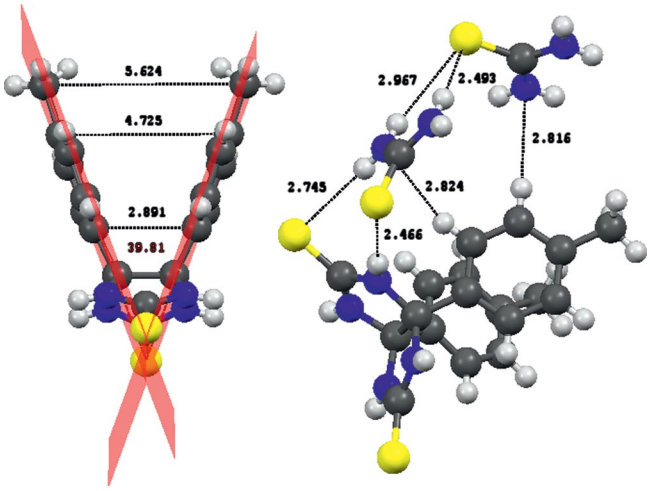


Figure 2. Molecular structure of **8**. (Left) Side view of the molecule showing the face-to-face interaction between the two aryl groups to form an angle of 39.8° and several distances between the planes, which increase along the *a* axis. (Right) Crystal structure of **8** and two molecules of thiourea with intermolecular interactions represented by dashed lines. For color coding, see Figure 1.

sional angle of N–C–C–N is 11.6°. This distortion results in a significant increase in the dihedral angle between the two tolyl groups (14.7 vs. 0.0° in **8**; Figure 3, left). Furthermore, the two rings are no longer parallel to one another. In **8**, the N1–C6a–C1$_{aryl}$–C2$_{aryl}$ and N3–C3a–C1′$_{aryl'}$–C2′$_{aryl'}$ dihedral angles are both 29°, and in **10** they are significantly different (35.8 and 16.2°, respectively). As was reported for the diphenyl analog,[31] the 1,3,5-oxadiazinane rings adopt a chair conformation, which thus pulls the two sulfur atoms closer to one another (5.80 Å in **10** rather than 6.70 Å in **8**). In contrast to the crystal structures of **3** and **8**, the crystal packing of **10** is no longer dominated by a network of

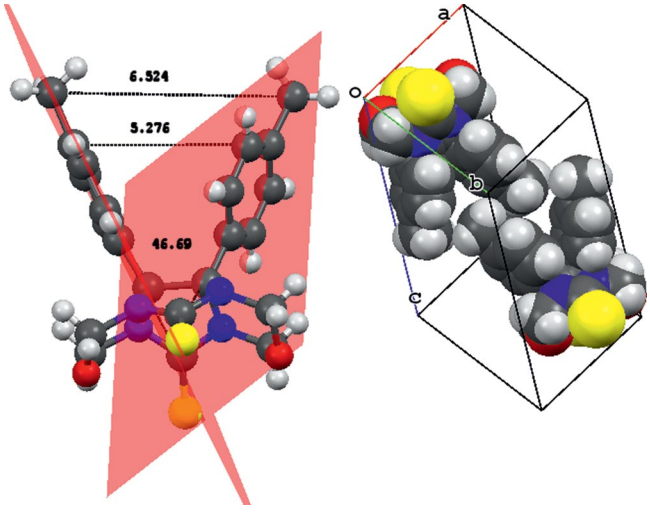


Figure 3. Molecular structure of **10**. (Left) Side view of the molecule showing the face-to-face interaction between the two aryl groups forming an angle of 46.7° and several distances between the planes. (Right) Space-filling presentation of two out of the four molecules of the unit cell, showing the hydrophobic interpenetrating interactions of the tolyl groups. For color coding, see Figure 1.

hydrogen bonds. In the absence of acidic protons on the nitrogen atoms, the packing is dictated by hydrophobic interactions, such as the interpenetration of the aromatic groups (Figure 3, right). Yet, there are significantly short contacts (2.45 and 2.67 Å) between the fully substituted nitrogen atoms and the *ortho*-hydrogen atoms on the aromatic rings.

It was already demonstrated that the oxygen analogs of diaryl thioglycoluril diether **10** are useful monomers in stepwise co-oligomerization reactions,[32] and Isaacs employed this strategy extensively for the construction of substituted cucurbiturils.[33] Yet, our attempts to employ the same conditions did not lead to the desired oligomerization. For example, treatment of **10** (2 equiv.) with either **8** or **1** (1 equiv.) in $MeSO_3H$ at 50 °C resulted in mixtures of decomposition products rather than any oligomers.

Conclusions

The key question at the basis of this study was why thiocucurbiturils were not reported during more than three decades of prolific research on cucurbituril chemistry. Although glycoluril is a highly stable, easily accessible precursor of all cucurbiturils, its sulfur analog **2** could not be prepared to date. We found that the reaction between glyoxal and thiourea stopped at the level of dihydroxyimidazolidine-2-thione (**5**). The latter was found to be quite unstable under various acidic conditions, and it rearranged into hydantoin and self-cleavage products. Several stable analogs of **2**, including **3**, **8**, and **10**, were prepared in the hope that they could be employed as building blocks for the synthesis of thiocucurbiturils. However, none of these analogs was sufficiently stable under the acidic conditions that were required for co-oligomerization with formaldehyde. Even prefabricated diether **10** could not stand the conditions for co-oligomerization with either thioglycoluril **8** or glycoluril (**1**).

Pichierri already predicted that thiocucurbiturils should be stable molecules.[9] DFT calculations anticipated that the portal diameter of thio-CB[6] would be only 0.1 Å broader and 0.5 Å higher than that of CB[6]. Given that it seems impossible to synthesize thiocucurbiturils by the same methods commonly used for the preparation of cucurbiturils, an alternative route must be designed. Thus, the problem is not how to keep the thiocucurbiturils alive, but how to make them. Alternative synthetic strategies that are different from the thermodynamically controlled approaches are currently being pursued in our laboratories. Their expectedly strong binding properties to specific metal ions and metal surfaces render the thiocucurbiturils an undoubtedly worthy synthetic target.

Experimental Section

General Remarks: All commercially available chemicals were purchased from Aldrich and used without further purification. TLC was performed on glass sheets precoated on silica gel. ^{1}H NMR and ^{13}C NMR spectra were performed in $CDCl_3$ and [D$_6$]DMSO

by using the residual solvent signals: $CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.2 ppm; [D_6]DMSO: δ_H = 2.5 ppm, δ_C = 39 ppm. NMR spectra were recorded with a AVIII400 Bruker spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz). IR spectra (KBr pellet) were recorded by using an FTIR Bruker Alpha spectrometer in the 400–4000 cm^{-1} range. Mass spectra and high-resolution mass spectra were recorded with a Waters LCT Premier microMax spectrometer (ESI-TOF, MeCN/H_2O = 7:3).

Crystal Structure Analysis: Crystals of **3**, **8**, and **10** were obtained by standing a period of time in ethanol solution. The single crystals were mounted in a Nonius KappaCCD diffractometer (for **8**) or APEX2 DUO diffractometer (for **3** and **10**) and data was collected by using graphite monochromatized Mo-K_α radiation (λ = 0.71073) at 293 K. The following programs were used for data collection and reduction: Nonius 1997 Collect,[34] HKL DENZO, and Scalepack.[35] Structures were solved by direct methods by using the maXus[36] program package and refined in the usual way by using SHELXL97.[37] Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically. CCDC-945330 (for **8**), -945332 (for **3**), and -945333 (for **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.il/data_request/cif. Pertinent crystallographic data and refinement parameters for **3**, **8**, and **10** are summarized in Table 3.

***cis*-/*trans*-4,5-Dihydroxyimidazolidine-2-thione (5):** A mixture of thiourea (3 g, 40 mmol), glyoxal (40% in H_2O, 2 mL, 20 mmol), and water (20 mL) was stirred at room temperature. After 30 min, the off-white precipitate separated out. The precipitate was filtered and dried under vacuum. Product *trans*-**5** was obtained as a pure off-white powder (2.3 g, 85%). IR (KBr): $\tilde{\nu}$ = 3300–3400 (OH), 3150–3250 (NH), 1617 (NH), 1474 (CN), 1414 (C=S) cm^{-1}. ^{1}H NMR ([D_6]DMSO): δ = 8.83 (br. s, NH, 2 H), 6.26 (d, J = 7 Hz, OH, 2 H), 4.72 (d, J = 7 Hz, CH, 2 H) ppm. ^{13}C NMR ([D_6]-DMSO): δ = 182.2, 87 ppm. HRMS [ESI(+)-TOF]: calcd. for $C_3H_7N_2O_2S$ [M + H]$^+$ 135.0228; found 135. 0226.

In a similar reaction performed at 65 °C, a mixture of *cis*/*trans* diastereoisomers of **5** was obtained, and the ratio was determined according to the ^{1}H NMR spectrum of the mixture. *cis*-**5**: ^{1}H NMR ([D_6]DMSO): δ = 8.56 (br. s, NH, 2 H), 5.81 (d, J = 7.6 Hz, OH, 2 H), 5.03 (d, J = 7.6 Hz, CH, 2 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 181.6, 80 ppm.

***trans*-4,5-Dimethoxyimidazolidine-2-thione (6):** Concentrated HCl was carefully added (0.2 mL) to a solution of *trans*-**5** (3 g, 40 mmol) in methanol (15 mL), and the mixture was heated at 50 °C. After 3 h, a white precipitate separated out. After filtration and drying under vacuum, **6** was obtained as a pure white solid (2.6 g, 40%). ^{1}H NMR ([D_6]DMSO): δ = 9.45 (br. s, NH, 2 H), 4.69 (s, CH, 2 H), 3.24 (s, OMe, 6 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 184.0, 91.7, 54.0 ppm. HRMS [ESI(+)-TOF]: calcd. for $C_5H_{10}N_2O_2S$ [M + H]$^+$ 163.0541; found 163.0529.

Monothioglycoluril (3): A mixture of **6** (0.49 g, 3 mmol) and urea (0.22 g, 3.6 mmol) in H_2O (20 mL) was stirred at 80 °C and concentrated HCl (0.2 mL) was carefully added. The reaction was kept at 80 °C for 2 h, and a fine, dark powder separated out during the reaction. Upon completion of the reaction (TLC), the insoluble black precipitate was filtered off. The clear aqueous solution was stored at 5 °C in the fridge overnight, which gave a pale brown crystalline solid as a mixture of **3** (90%) and **1** (10%). Recrystallization from aqueous HCl afforded **3** as a brownish solid (0.22 g, 45%); m.p. 300–302 °C. IR (KBr): $\tilde{\nu}$ = 3200–3450 (NH), 1713 (C=O), 1617 (NH), 1512 (CN), 1110 (C=S) cm^{-1}. ^{1}H NMR ([D_6]-DMSO): δ = 8.93 (s, 1 H), 7.42 (s, 1 H), 5.41 (s, 1 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 182.58, 160.8, 68.6 ppm. HRMS [ESI(+)-TOF]: calcd. for $C_4H_6N_4OS$ [M + H]$^+$ 159.0341; found 159.0332.

General Procedure for the Synthesis of 7–9: A mixture of 4,4′-dimethylbenzil (240 mg, 1 mmol), thiourea (305 mg, 4 mmol), and KOH (34 mg, 0.6 mmol) in *t*BuOH (4 mL) was sonicated in an ultrasonic bath (40 kHz), and the mixture was irradiated at 55 °C for 2 h. After solvent evaporation, water was added (20 mL) to the resultant white solid, and the heterogeneous mixture was sonicated for 15 min and then filtered. The resulting white powder was washed thoroughly in cold water and dried to afford 3a,6a-bistolylthioglycoluril (**8**) as a pure white powder (280 mg, 78%); m.p. >300 °C (decomp.). The clear aqueous filtrate was concentrated under reduced pressure to afford a light yellow solid identified as pure 4,5-dihydroxy-4,5-bistolylimidazolidine-2-thione (**7**; 35 mg, 11%); m.p. 168–170 °C. Upon neutralizing the filtrate with acetic acid, precipitation occurred immediately, and the solid was collected. After washing in water and drying under vacuum, hydantoin **9** was isolated as a pure white powder (33 mg, 11%); m.p. 200–202 °C.

4,5-Dihydroxy-4,5-bistolyl-imidazolidine-2-thione (7): ^{1}H NMR ([D_6]DMSO): δ = 7.20 (d, J = 8 Hz, 4 H), 7.06 (d, J = 8 Hz, 4 H), 2.25 (s, 6 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 183.8, 139.4, 135.6, 128.2, 126.9, 72.7, 20.6 ppm. HRMS [ESI(+)-TOF]: calcd. for $C_{17}H_{18}N_2O_2S$ [M + H]$^+$ 315.1167; found 315. 1153.

3a,6a-Bistolylthioglycoluril (8): IR (KBr): $\tilde{\nu}$ = 3100–3300 (NH), 1543 (CN), 1495 (C=C), 1208, 1085 (C=S) cm^{-1}. ^{1}H NMR ([D_6]-DMSO): δ = 9.71 (br. s, 4 H), 6.93 (d, J = 8 Hz, 4 H), 6.83 (d, J = 8 Hz, 4 H), 2.12 (s, 6 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 182.3, 137.7, 132.6, 128.2, 126.8, 89.6, 20.5 ppm. HRMS [TOF(+)-ESI]: calcd. for $C_{18}H_{18}N_4S_2$ [M – H]$^+$ 353.0895; found 353.0876.

5,5-Bistolyl-2-thione-4-imidazolidone (9): IR (KBr): $\tilde{\nu}$ = 3050–3150 (NH), 1737 (C=O), 1524 (CN), 1188, 1165 (C=S) cm^{-1}. ^{1}H NMR ([D_6]DMSO): δ = 12.08 (s, 1 H), 11.24 (s, 1 H), 7.21 (d, J = 8 Hz, 4 H), 7.16 (d, J = 8 Hz, 4 H), 2.29 (s, 6 H) ppm. ^{13}C NMR ([D_6]-DMSO): δ = 181.62, 175.9, 138.2, 136.06, 129.7, 126.9, 73.2, 20.1 ppm. HRMS [TOF(+)-ESI]: calcd. for $C_{18}H_{18}N_4S_2$ [M – H]$^+$ 295.0905; found 295.0908.

Compound 10: A mixture of **8** (0.7 g, 2 mmol), paraformaldehyde (0.24 g, 8 mmol), and concentrated HCl (20 mL) was heated at 100 °C for 24 h. After being cooled to room temperature, the product precipitated out of the cold solution. The solid was filtered off, washed with water, and finally dried under vacuum. Thus, **10** was obtained as a white crystalline (0.72 g, 82%); m.p. >300 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ = 6.97 (s, 8 H), 6.22 (d, J = 10.4 Hz, 4 H), 4.77 (d, J = 10.8 Hz, 4 H), 2.21 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 186.2, 139.8, 129.7, 128.6, 127.5, 86.6, 75.1, 21.0 ppm. HRMS [ESI(+)-TOF]: calcd. for $C_{22}H_{22}N_4O_2S_2$ [M + H]$^+$ 439.1262; found 439.1250.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra of **3**, *trans*-**5**, and **6**–**10**.

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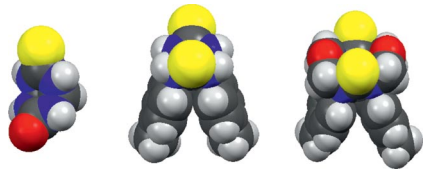
Although glycoluril is a highly stable, easily accessible precursor of all cucurbiturils, dithioglycoluril is still unknown. To answer the question why thiocucurbituril has never been made, we prepared several thioglycoluril derivatives and found that they do not survive the acidic conditions usually needed for the co-oligomerization reaction with paraformaldehyde.



Keywords: Building blocks / Dicarbonyls / Hydantoin / Macrocycles / Sulfur

