

Full Paper

Synthesis and X-ray Structure of the Inclusion Complex of Dodecamethylcucurbit[6]uril with 1,4-Dihydroxybenzene

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Abstract: The synthesis, and X-ray crystal structure of the inclusion host-guest complex of dodecamethylcucurbit[6]uril (DDMeQ[6]) with 1,4-dihydroxybenzene (DHOBEN) are reported. The complex crystallizes in the space group P21/c (No.14) with $a = 12.2847(4)$, $b = 12.6895(4)$, $c = 15.1310(4)$ Å, $\alpha = 74.6960(10)$, $\beta = 71.4090(10)$, $\gamma = 86.5090(10)^\circ$ and $Z = 1$. A novel approach to dodecamethylcucurbit[6]uril synthesis is also described. To separate dodecamethylcucurbit[6]uril, 1,4-dihydroxybenzene is used as a guest molecule for crystallization of the fully methyl-substituted cucurbituril. The driving force for the self-assembled inclusion host-guest complex can be attributed to not only the cavity interaction of dodecamethylcucurbit[6]uril (host), but also to the hydrogen bonding between the carbonyl oxygen at the portals of the host and the hydroxy groups of the guest.

Keywords: Dodecamethylcucurbit[6]uril, inclusion host-guest complex, crystal structure.

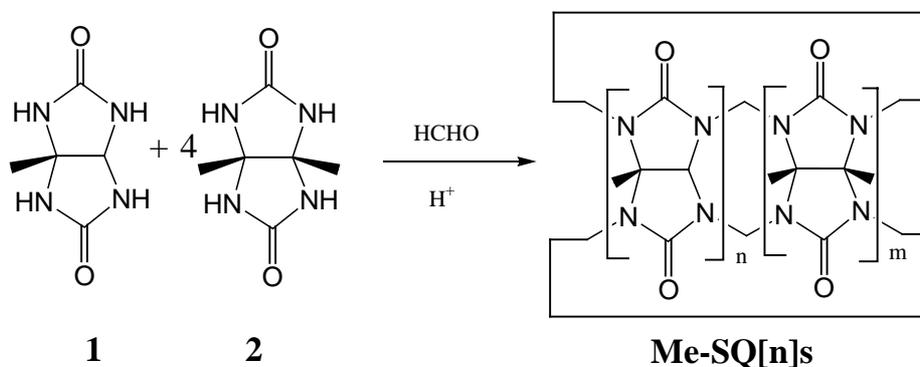
Introduction

The chemistry of cucurbit[n]uril (Q[n]s) has expanded dramatically with the discovery of cucurbituril(Q[6]) and its homologues (Q[5], Q[7], Q[8], and Q[10]) [1-3]. Recently, the direct functionalization of CB[n][4-6] and introduction of building blocks for the preparation of Q[n] derivatives[7-9] and analogues[10-11] providing CB[n]s with solubility in both organic and aqueous solution has further expanded the range of the research and applications, which have been summarized

in related reviews [12-19]. More recently, we have found that the solubilities of substituted cucurbit[n]urils (SQ[n]s) are dependent upon the kind, position and number of substituent groups on the substituted cucurbit[n]urils Q[n]s [20].

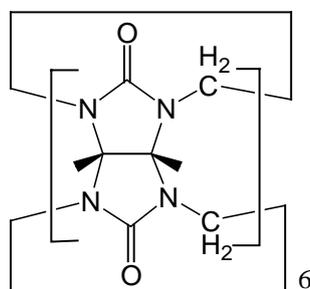
Since the discovery in 1992 of the first substituted Q[n], decamethylcucurbit[5]uril, Me₁₀Q[5] [21], a number of fully and partially substituted Q[n]s have been reported since 2001. An approach to partial methyl substituted cucurbit[n]urils was demonstrated by Day in 2003 [8]. In this work, a similar approach to substituted cucurbituril synthesis is reported (Scheme 1), whereby one mole equivalent of monomethylglycoluril (**1**) was added to four mole equivalent of dimethylglycoluril (**2**) in 12 M HCl with the addition of formaldehyde to produce a mixture of methyl-substituted cucurbit[n=5,6]urils (Me-SQ[5, 6]).

Scheme 1. Synthesis of methyl-substituted cucurbit[n]urils.



From this mixture a very rare dodecamethylcucurbit[6]uril (DDMeQ [6] shown in Scheme 2) can be obtained in moderate yield (compared to the yield of 0.2% in the literature method [22]). The crystal structure of DDMeQ[6] has been characterized for the first time as the inclusion host-guest complex of dodecamethylcucurbit[6]uril (DDMeQ[6], host) and 1,4-dihydroxybenzene (DHOBEN, guest).

Scheme 1. Structures of DDMeQ[6].

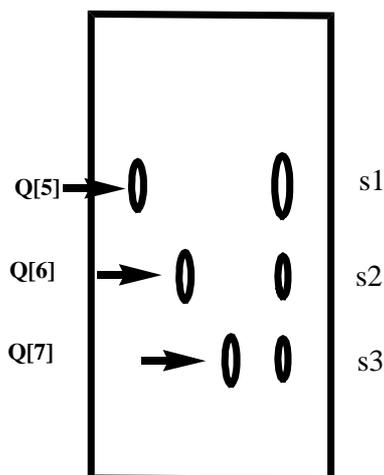


Results and Discussion

The TLC analysis showed three well separated spots with a ratio of 3(s1):1(s2):1(s3), which corresponded to the normal cucurbit[5, 6, 7]urils (Q[5], Q[6], Q[7], Figure 1). The typical guest probe tests showed that the substituted s3 cucurbit[n]uril(s) were not SQ[7], but rather SQ[6], because no included 1-adamantaneamine (ad) resonance signals were observed in the $^1\text{H-NMR}$ spectrum of the s3-ad system [23], while the $^1\text{H-NMR}$ spectra exhibited two sets of signals for the bound (indicated by wedges) and unbound protons of the HCl salt of 2,2'-bipyridine (bpy·1HCl) which suggested that the s3 was definitely SQ[6]s [24].

To isolate the DDMeQ[6] from s3, various guests were used for crystallizing DDMeQ[6] and the DDMeQ[6]-DHOBEN system was the first one in which the single crystals of DDMeQ[6] adduct with DHOBEN were obtained by dissolving DDMeQ[6] in a solution of DHOBEN in water. The final solution was mixed thoroughly and allowed to stand at room temperature; crystals formed after several days, and were collected.

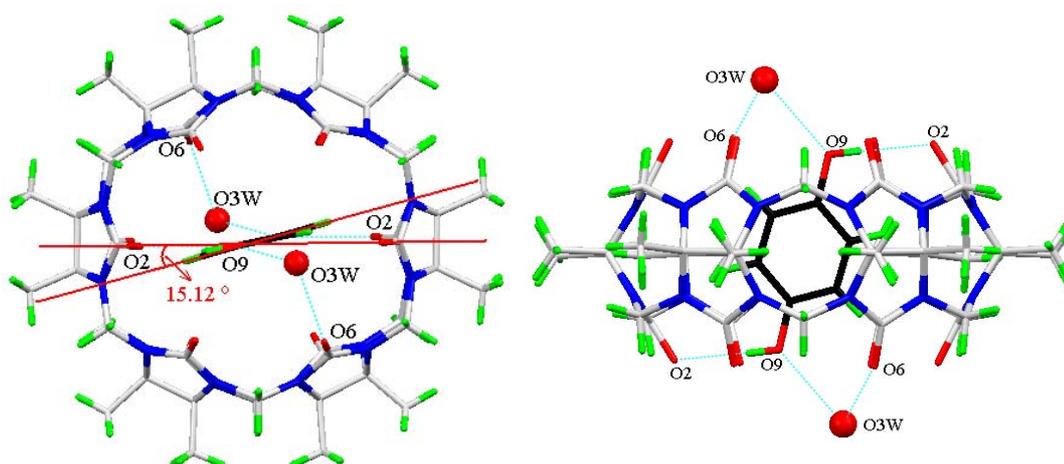
Figure 1. The TLC profile of the mixture of the substituted Qs (I_2 as a visualization agent).



The crystal structure of inclusion host-guest complex of DDMeQ[6] with DHOBEN has been determined by single crystal X-ray diffraction at 223K. The complex crystallizes in the triclinic space group P21/c (No.14) with cell dimensions: $a = 12.2847(4) \text{ \AA}$, $b = 12.6895(4) \text{ \AA}$, $c = 15.1310(4) \text{ \AA}$, $\alpha = 74.6959(10)^\circ$, $\beta = 71.4090(10)^\circ$, $\gamma = 86.5090(10)^\circ$. Figure 2 shows two views of the DDMeQ[6]-DHOBEN inclusion complex. In the solid state, the whole DHOBEN molecule is clearly included in the cavity center of the DDMeQ[6] host. It is notable that a preferential orientation of two OH groups of the guest protruding towards the portal of DDMeQ[6] will cause a obvious distortion of the host, so the macrocycle is not circular but an ellipsoid. The distance between the portal carbonyl oxygens O1 and O3 is about 5.681 \AA , and between O4 and O6 it is about 5.853 \AA , while the distance between the portal carbonyl oxygens O2 and O5 is up to 7.091 \AA , which is approximately about 20% longer than the closer sides. In addition, the guest is inserted to the extent that the aromatic ring sits essentially in line with opposite sets of oxygen donors O2 and O5, but is twisted away from linearity by $\sim 15.0^\circ$ (referring to Figure 2, top view). Moreover, the formation of hydrogen bonds between the OH groups of DHOBEN with the portal rimmed carbonyls of DDMeQ[6] increases the stability of the title inclusion complex. The main hydrogen bonds are O9-H9...O2, O3W-H3W...O9, and O3W-H3W...O6,

the distances are 2.828, 2.703 and 2.929 Å. Thus, in the self-assembled structure of the inclusion complex of DDMeQ[6]- DHOBEN, the main driving forces can be attributed to the hydrophobic interaction between the cavity of DDMeQ[6] and aromatic moiety of the DHOBEN, and the hydrogen bonds between the hydroxyl group of the guest and the carbonyl oxygen atom(s).

Figure 2. Crystal structure of the inclusion host-guest complex of DDMeQ[6]-DHOBEN, showing partial atomic numbering and drawn at the 50% probability level in top view(left) and side view(right).



Acknowledgements

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Experimental

General

All reagents and chemicals were obtained from Beijing Chemical Company (P.R. China) and used without further purification. Column chromatography elution was carried out with formic acid (HCOOH, $\geq 88\%$) and acetic acid (CH₃COOH, $\geq 99.5\%$) at different ratios. ¹H- and ¹³C-NMR spectra were recorded on an INOVA-400 (Varian, 400 MHz) spectrometer. The solvent used was D₂O. ES-MS measurements were performed on an HP 1100 LC-MSD at room temperature.

Syntheses and separation

12M HCl (350 mL) was added to a mixture of monomethylglycoluril (6.44 g, 0.04 mol), dimethylglycoluril (27.2 g, 0.16 mol) and paraformaldehyde (15.0 g), and the mixture was stirred at room temperature for approx ~30 min (at which point all solids dissolved) and then heated at 90°C for 8 hr to give a brown coloured solution, which was allowed to cool to room temperature, and then the acidic solvent was evaporated *in vacuo* to give a crude brown solid (38~41 g). The solid was dissolved

in water (85 mL) and this solution was added dropwise to acetone (1000 mL) with vigorous stirring. The yellow precipitate formed was collected by filtration and air dried to give a yellow-red mixture of methyl substituted SQ[n]s 34~373g, yield: 69.9~76.7% (based on starting materials). TLC analysis on a silica gel plate showed that the mixture of methyl substituted SQ[n]s obtained can be readily separated into three bands (s1, s2 and s3) by elution with HCOOH/CH₃COOH (1:2, v/v), compared to the normal Q[5], Q[6] and Q[7]; the ratio of s1:s2:s3 was ~60:20:20. A mixture of the substituted Qs (20 g) was loaded onto a silica gel column (200-300 mesh, 90 cm x 8.0 cm) and eluted with HCOOH/CH₃COOH (1:1 ~ 1:2 v:v), to give a total of 10.1 g of s1, 3.4 of s2 and 3.5 g of (overall yield: ~ 85%). To isolate the DDMeQ[6] from s3, a series of guest molecules such as dioxane, 2,2'-bipyridine, 5,5'-dimethyl-2,2'-bipyridine, 1, ω -alkylenediamines *etc.* were used for attempted crystallization of DDMeQ[6]. Single crystals of DDMeQ[6]@DHOBEN were obtained by adding 1,4-dihydroxybenzene (DHOBEN, 0.058 g, 0.53 mmol) to a solution of DDMeQ[6] (0.50 g, 0.43 mmol) in water (12 mL). The final solution was mixed thoroughly and allowed to stand at room temperature; crystals formed after several days and were collected by filtration.

X-ray analysis of inclusion complex

The data were collected on a Bruker Apex-2000 CCD diffractometer at 223 K, using graphite monochromated Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$) with ω scan mode. Lorentz polarization and absorption corrections were applied. Structural solution and full matrix least-squares refinement based on F^2 were performed with the SHELXS-97 and SHELXL-97 program package, respectively. All the non-hydrogen atoms were refined anisotropically. H atoms were placed in calculated positions and refined using a riding model, with isotropic thermal parameters equal to 1.2-1.5 times those of their parent atoms. In the final cycles of refinement, least squares weights of the form $w = 1/[\sigma^2(F_o)^2 + (aP)^2 + bP]$, $P = [\max(F_o^2, 0) + 2F_c^2]/3$ were employed ($a = 0.1328$, $b = 2.2163$). The ORTEP-3 [12] and WebLab programs were used for illustrations. Crystallographic data for DDMeQ[6] are listed in Table 1. CCDC 633953 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 1. Crystallographic parameters for DDMeQ[6].

Chemical formula	C ₇₈ H ₉₀ N ₂₄ O ₃₆
Formula weight	139.74
Crystal Color, Habit	colorless, diamond like
Crystal Dimensions	0.1 × 0.1 × 0.15
Crystal System	triclinic
Lattice Type	primitive
Space Group	P-1
Lattice Parameters	$a = 12.2847(4) \text{ \AA}$
	$b = 12.6895(4) \text{ \AA}$
	$c = 15.1310(4) \text{ \AA}$
	$\alpha = 74.6960(10)^\circ$
	$\beta = 71.4090(10)^\circ$
	$\gamma = 86.5090(10)^\circ$
Volume	2155.66(11) \AA^3

Table 1. Cont.

Z value	1
D _{calc}	1.494 g/cm ³
F(000)	1014
μ (MoK α)	0.120 mm ⁻¹
Reflections/restraints/parameters	7477 / 0 / 640
Residuals: R1, wR2 [I > 2 σ (I)]	0.0767, 0.2216
Goodness of Fit, S	1.079
Max. shift/error	0.000
Max. peak in final Δρ synthesis	0.825
Min. peak in final Δρ synthesis	-0.812

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Sample availability: Contact the authors.