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Twisted Cucurbit[*n*]urils

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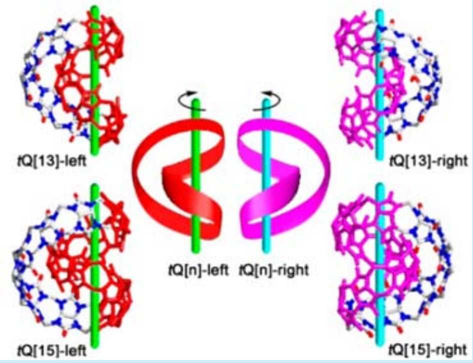
Supporting Information

ABSTRACT: Two new twisted cucurbiturils, cucurbit[13]uril (*t*Q[13]) and cucurbit[15]uril (*t*Q[15]), have been synthesized and separated, and their structures have been confirmed by NMR spectroscopy and MALDI-TOF mass spectrometry together with the X-ray structures of two new complexes, $\{Dy(H_2O)_4Cd(H_2O)_4tQ[13]\}\cdot 2.5[CdCl_4]\cdot 65H_2O$ and $\{Cd_{0.5}(H_2O)_2tQ[15]\}\cdot[CdCl_4]\cdot 47H_2O$. *t*Q[15] is the largest cucurbit[*n*]uril (Q[*n*]) in the Q[*n*] family reported to date. The X-ray diffraction studies of both complexes indicated that these large *t*Q[*n*]s effectively exhibit two different cavities—a central cavity and two side cavities. Preliminary host—guest behavior by each of the new systems was investigated by NMR studies.



Over the last three decades, the cucurbit[*n*]uril family of macrocycles has continued to receive considerable attention, motivated by potential applications, including as new materials for wastewater remediation,[1] as receptors for a range of host—guest separation processes,[2] and as artificial enzymes.[3] Although the cucurbit[$n \leq 10$]uril family has now been well developed and explored,[4−18] only a limited number of Q[$n > 10$] derivatives have been isolated and investigated,[19,20] as the preparation and successful separation of these larger Q[*n*] systems have remained a significant challenge. Examples include hemicucurbit[12][19] and the twisted cucurbit[14]uril (*t*Q[14]) (which is formed from 14 $-glycoluril-(CH_2)_2-$ moieties and exhibits a 180° twist, giving rise to enantiomeric forms).[20] Over recent years some basic questions have arisen concerning Q[*n*] synthesis and separation. First, is it possible to synthesize and isolate the "missing" larger cucurbit[*n*]urils, and second, at what point do "normal" Q[*n*]s switch to a twisted form? Does the formation of *t*Q[*n*]s occur through a chain-growth process, as is commonly found in polymer chemistry,[21,22] or by a step-growth process as suggested by Isaacs?[17] With respect to this, it was anticipated that a consideration of the lengths of the oligomer precursors might yield some useful information. In part, the above considerations provided a motivation for undertaking the present study.

As an extension of our previous studies on *t*Q[14],[20] we now describe the preparation and separation of two new twisted cucurbit[*n*]urils, *t*Q[13] and *t*Q[15], using moderate reaction conditions. Initially, we performed a test synthesis employing a 1:2 glycouril:formaldehyde ratio in 9 M HCl solution at 60 °C for 2 days. A matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) spectrum of the reaction precipitation showed the presence of numerous intermediates and oligomers of glycouril, including the glycouril pentadecamer (Figure S1 in the Supporting Information (SI)). Unfortunately, when the mixture was subjected to Dowex ion-exchange chromatography, only Q[5] and Q[6] with a minor amount of Q[7][4−6] were collected, suggesting that the larger intermediates formed were slowly transformed into smaller "normal" Q[*n*]s. Although the above separation process did not yield the expected long-chain oligomers, it prompted us to try to obtain larger Q[*n*]s under more moderate reaction conditions. In a subsequent synthesis, generally similar reaction conditions were employed except that the reaction temperature

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was increased to 90 °C and the reaction time was reduced to 6 h. A mixed product precipitate was formed from the reaction solution upon addition of methanol. This was washed with hot water to give a water-soluble fraction. While this contained mainly Q[5] and Q[7], further species were also separated by means of Dowex ion-exchange chromatography involving an eluting time of many months (see the SI). A mixture incorporating at least three larger Q[*n*]s was collected. Further separation by thin-layer chromatography (TLC) gave three separated bands corresponding to compounds **b1**, **b2**, and **b3**, respectively (Figure S2). Comparison of *t*Q[14] with the developed bands showed that **b2** corresponded to this cucurbituril, while it was predicted that **b1** might be a new Q[*n*] smaller than *t*Q[14] while **b3** could be also a new Q[*n*] larger than *t*Q[14], which would make it the largest member of the Q[*n*] family reported to date.

Similar to *t*Q[14], **b1** and **b3** show solubility in both water and DMSO. Their ^{1}H NMR spectra in D_2O were in accord with them being typical symmetrical Q[*n*]s; they display three groups of proton resonances of about 1:1:1 relative intensity. For **b1**, doublets occur at δ 4.11 and 5.56, while a singlet occurs at δ 5.37; for **b3**, the doublets occur at δ ~4.10 and 5.62 and the singlet at δ 5.37 (Figure 1a,b). However, the corresponding proton resonances for **b1** and **b3** in DMSO-d_6 are somewhat broadened (Figure 1c,d). The ^{13}C NMR spectra in D_2O show three sharp resonances at δ 52.51, 70.47, and 155.89 for **b1** and at δ 53.11, 71.96, and 156.28 for **b3** (Figure 2). Because of the limited solubility of **b1** and **b3** in DMSO-d_6, satisfactory ^{13}C NMR spectra cound not be obtained. As expected, ^{1}H NMR studies of samples held at 70 °C for 3 h in both concentrated DCl (35%) and NaOD (0.01 M) indicated that both *t*Q[*n*]s are stable under these experimental conditions.

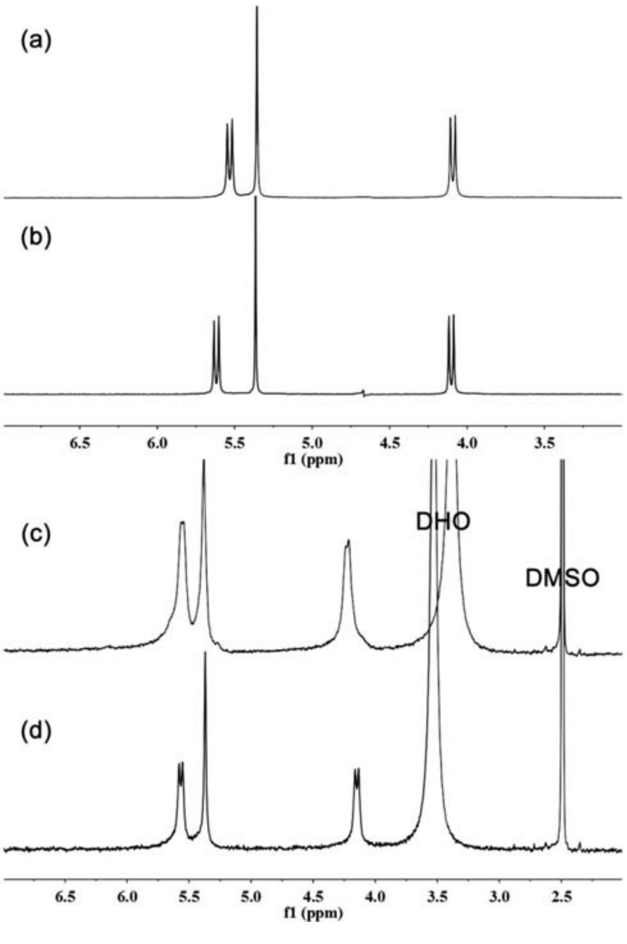

Figure 1. ^{1}H NMR spectra of (a, c) **b1** and (b, d) **b3** in (a, b) D_2O and (c, d) DMSO-d_6.

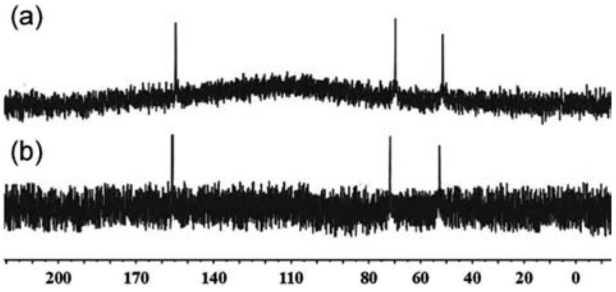

Figure 2. ^{13}C NMR spectra of (a) **b1** and (b) **b3** in D_2O.

MALDI-TOF analysis of the new Q[*n*]s gave ions that were equivalent to Q[13] and Q[15] species (for the Q[13]-Na ion, *m*/*z* = 2182, and for Q[15]-K ion, *m*/*z* = 2529), as shown in Figures S3 and S4.

Subsequently, two metal complexes, *t*Q[13]-Dy^{3+}/Cd^{2+} and *t*Q[15]-Cd^{2+}, were successfully synthesized using a $[CdCl_4]^{2-}$ anion-induced strategy,[23] and small crystals of each were obtained. Both structures were solved using a synchrotron X-ray source. The structures unambiguously showed complexes incorporating twisted Q[*n*]s; one is of type $\{Dy(H_2O)_4Cd(H_2O)_4tQ[13]\}\cdot 2.5[CdCl_4]\cdot 65H_2O$ (**1**), while the other is of type $\{Cd_{0.5}(H_2O)_2tQ[15]\}\cdot[CdCl_4]\cdot 47H_2O$ (**2**). The latter contains *t*Q[15], the largest member in the Q[*n*] family reported to date.

Interestingly, the crystal structure of **1** shows a further example of the now well-documented "honeycomb effect" associated with the presence of $[CdCl_4]^{2-}$ anions.[24] These surround the *t*Q[13] molecule and involve ion−dipole interactions between the anions and the electropositive outer surface of the *t*Q[13] via so-called "outer surface" interactions. The structure is a heterometallic one-dimensional coordination polymer (Figure S5). Moreover, the *t*Q[13] molecules in the same coordination polymer chain have the same helicity; each chain is surrounded by six other chains, with two of these incorporating *t*Q[13] molecules with the same helicity while the remaining four show opposite helicity. Each *t*Q[13] unit coordinates with three metal ions: one Cd^{2+} cation (Cd1) coordinates to four carbonyl oxygens (O6, O7 and O15, O16), two located on each portal of a *t*Q[13] molecule, and two Dy^{3+} cations link neighboring *t*Q[13]-Dy^{3+}/Cd^{2+} units (Figure 3a) to form a linear heterometallic-complex-based coordination polymer (Figure S5c,d). Unlike related (nontwisted) Q[*n*] systems, which are generally surrounded by six $[CdCl_4]^{2-}$ anions, each *t*Q[13] molecule in the present complex is surrounded by 11 anions, undoubtedly a reflection of its helical conformation. As is common in Q[*n*] metal coordination chemistry, the negative environment at the portals of the *t*Q[13] molecule leads to this host readily coordinating to metal centers to form a linear coordination polymer (Figures 3a and S5 and Tables S1 and S2).

Crystals of **2** were obtained from an aqueous HCl solution containing $CdCl_2$. However, the X-ray crystal structure shows no $[CdCl_4]^{2-}$-based honeycomb structure in this case: instead, each *t*Q[15]/Cd^{2+} complex is associated with four $[CdCl_4]^{2-}$ anions. The structure of the *t*Q[15]/Cd^{2+} complex is shown in

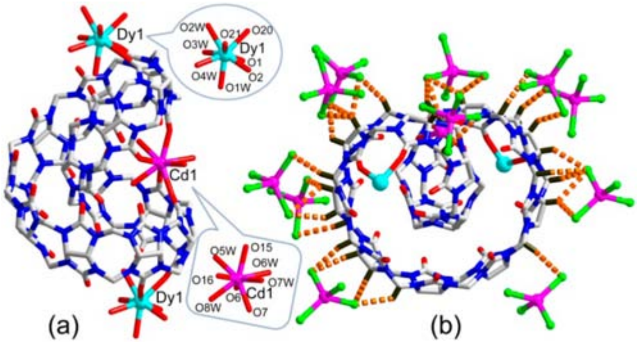

Figure 3. X-ray crystal structure of **1**: (a) interactions between the Dy^{3+}/Cd^{2+} ions and a *t*Q[13] molecule; (b) interactions between a *t*Q[13] molecule and the [CdCl$_4$]$^{2-}$ anions.

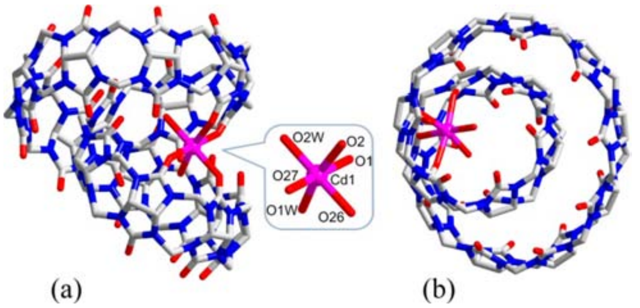

Figure 4. X-ray crystal structure of **2**: (a) side view and (b) top view of the Cd^{2+}/*t*Q[15] complex.

Figure 4. In this complex, the Cd1 cation coordinates to four carbonyl oxygens from both portals of the *t*Q[15] molecule (O1, O2 and O26, O27). Such coordination behavior is clearly unique to *t*Q[*n*]s.[20] The assembly of the Cd^{2+}/*t*Q[15] complex shows that the *t*Q[15] molecules have the same helical twist in alternative Cd^{2+}/*t*Q[15] complex layers along the *c* axis, with the [CdCl$_4$]$^{2-}$ anions sandwiched between the complex-based layers (Figure S6 and Tables S1 and S2).

Three typical guest compounds of different dimensions, the hydrochloride salts of hexamethylenediamine, 4,4′-bipyridine, and amantadine, were selected to probe host−guest formation by **b1** and **b3**. The results from ^{1}H NMR titrations are in accord with all three guests interacting with both of the new Q[*n*]s and indicate the presence of fast exchange on the NMR time scale (only one set of host and guest proton resonances were observed in each case) (Figures S7−S12). The proton resonances for the respective guests show different upfield shifts, with the upfield shifts for **b3** in general being larger than the corresponding shifts for **b1**, tentatively suggesting that the cavity in **b3** provides a better "fit" for all three guests.

We now consider the novel structure features of the *t*Q[*n*]s. It should be noted that the *t*Q[*n*]s exhibit chirality due to their helical nature and hence will form as enantiomers.[25] Actually, a *t*Q[*n*] can be read as a construction of two helices with the same pitches and reversed helical directions, one being a central helix with a smaller section and the other one being an outer helix with a larger section. The most interesting structural feature could be the central helix; when a helical *t*Q[*n*] is resolved, in principle the individual enantiomers could be employed to recognize chiral species.

Moreover, the central helix can be seen to define the central cavity of a *t*Q[*n*] (green area in Figure 5a,b), and the space between the central helix and the outer helix defines the two side cavities of the *t*Q[*n*] molecule (blue and yellow areas in Figure 5c,d), leading to the prospect of *t*Q[*n*]s presenting special guest identification properties. Thus, a guest could be accommodated in the central cavity or in the two side cavities. A recent study involving *t*Q[14] supports such a prospect.[26]

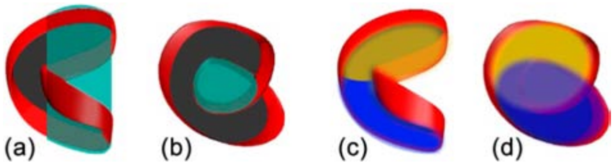

Figure 5. Central cavity and side cavities in a *t*Q[*n*].

In general, *t*Q[*n*] molecules are expected to maintain a high affinity for metal ions because their twisted configuration upon complex formation allows a more concentrated carbonyl oxygen distribution at the metal binding sites (see Figures 3 and 4).[20]

In summary, we have isolated and characterized two new *t*Q[*n*]s, *t*Q[13] and *t*Q[15], the latter becoming the largest reported member of the Q[*n*] family. Although the discovery of *t*Q[13] and *t*Q[15] does not absolutely answer the question concerning the point at which normal Q[*n*]s transform to *t*Q[*n*]s, it does indicate that this should occur at either Q[11] or Q[12]. Like large-ring cyclodextrins,[27−30] the large Q[*n*]s clearly also show a strong tendency to form *t*Q[*n*]s, with the central helix perhaps playing a role as a self-template to prevent the flexibility of long oligomers formed from chain-growth or step-growth processes. Formation of the central helix leads to Q[*n*] derivatives that display effectively reduced portal sizes and cavity volumes, which could enable them to display properties such as chiral recognition, novel host−guest interactions, and unusual metal coordination behaviors as well as to exhibit enhanced solubility in a range of solvents (including water and DMSO). More detailed investigations of resolution, the host−guest chemistry, and the metal coordination chemistry of the new *t*Q[*n*]s are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01842.

Experimental and characterization details and additional figures (PDF)
Crystallographic data for **1** (CIF)
Crystallographic data for **2** (CIF)

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Notes

The authors declare no competing financial interest.

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