Organic LETTERS

Letter

pubs.acs.org/OrgLett

Mono- and Dihydroxylated Symmetrical Octamethylcucurbiturils and Allylated Derivatives

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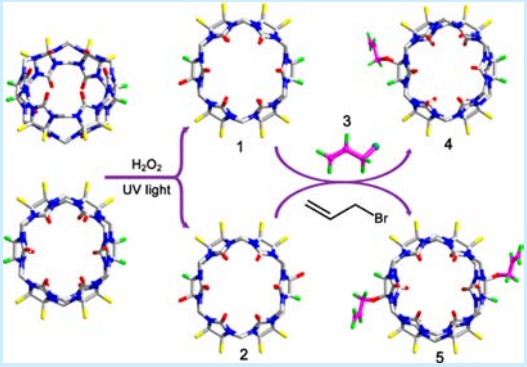
Supporting Information

ABSTRACT: Mono- and dihydroxylated symmetrical octamethylcucurbit[6]urils {(OH)OMeQ[6] and $(OH)_2$OMeQ[6]} were prepared using a photochemical method to introduce limited alcohol group(s) directly to the parent symmetrical octamethylcucurbit[6]uril (OMeQ[6]), and the resulting compounds were verified by ^{1}H NMR, Xevo Q-TOF MS, and X-ray crystallography. Further chemical modification of mono- and dihydroxylated OMeQ[6] was also performed.



Cucurbit[*n*]urils (Q[*n*]s)[1] are characterized by their hydrophobic cavities and hydrophilic portals, two main branches of Q[*n*] chemistry have emerged, namely, Q[*n*]-based host guest chemistry[2−14] and Q[*n*]-based coordination chemistry.[15−20] A high chemical stability prevents the easy preparation of functionalized Q[*n*]s in high purity and through efficient conversion, particularly, for larger Q[*n*]s and alkyl substituted Q[*n*]s. In 2003, Kim and co-workers made a landmark breakthrough in the synthesis of Q[*n*] derivatives by preparing a series of perhydroxylated cucurbit[*n*]urils {$(HO)_{2n}$Q[*n*]s},[21] and this served as a trigger for the synthesis of many other functionalized cucurbit[*n*]urils.[22−27] Perhydroxylated cucurbit[*n*]urils [$(HO)_{2n}$Q[*n*](n = 5−8)] were obtained by direct oxidation of the corresponding Q[*n*]s with $K_2S_2O_8$ in water. However, this reaction is only moderately efficient for Q[5] and Q[6] (yields of 42 and 45%, respectively) and almost impracticable for larger Q[*n*]s such as Q[7], Q[8] (ca. 5%), and alkyl substituted Q[*n*]s. Although a straightforward procedure for introducing one or more points of chemical attachment on the outer surface of perhydroxylated cucurbit[*n*]urils {$(HO)_{2n}$Q[*n*]s} is possible in principle, this would not guarantee a high level of control over molecular structures unless mono- or dihydroxylated cucurbit[*n*]urils ({(HO)Q[*n*]-s} and {$(HO)_2$Q[*n*]s}) were used in such a procedure. Two routes have been reported for the synthesis monofunctionalized Q[*n*]s. Isaacs and co-workers reacted C-type oligomers, such as the C-hexamer precursor, with a suitably functionalized glycoluril to afford a monofunctional Q[7] in a five-step sequence,[24−26,28] whereas Scherman and co-workers prepared monohydroxycucurbit[6]uril using persulfate salts[22] in a method modified from that described by Kim.[21] However, reaction conversions are not quantitative and require nontrivial and time-consuming purification steps. Moreover, these methods are not generally applicable to cucurbit[*n*]urils (Q[*n*]s) such as Q[8], or to alkyl-substituted cucurbit[*n*]urils (SQ[*n*]s). Recently, Bardelang and Ouari developed a photochemical method to introduce a limited alcohol functional group directly to cucurbit[*n*]urils (n = 5, 6, 7, 8) using hydrogen peroxide and UV light.[29] Although they have since corrected the conversions from 95−100% to 20−40%,[30] this method is still efficient enough for oxidation of larger Q[*n*]s such as Q[7] and Q[8], or for alkyl-substituted Q[*n*]s, which have never been successfully oxidized in our laboratory.

Alkyl-substituted cucurbit[*n*]urils (Q[*n*]s), especially those with alkyl-substituted groups at certain positions, could yield special oxidation products if OH group(s) could be introduced at designated position(s). In the present work, a symmetrical octamethylcucurbituril (OMeQ[6]) was selected as parent SQ[*n*][31] and reacted to form monohydroxylated OMeQ[6] {(OH)OMeQ[6], **1**} and dihydroxylated OMeQ[6] mixture containing major {*trans*-$(OH)_2$OMeQ[6], **2**} and minor {*cis*-$(OH)_2$OMeQ[6]. Moreover, mono- and trans-diallylated OMeQ[6]s (**4** and **5**) were also prepared by reaction of **1** and **2** with allyl bromide (**3**), respectively. Thus, SQ[*n*]s could

Received: September 16, 2016
Published: October 21, 2016

DOI: 10.1021/acs.orglett.6b02789
Org. Lett. 2016, 18, 5544−5547

be activated at designated position(s), and this could provide a new route for further functionality (Figure 1 and Scheme S1).

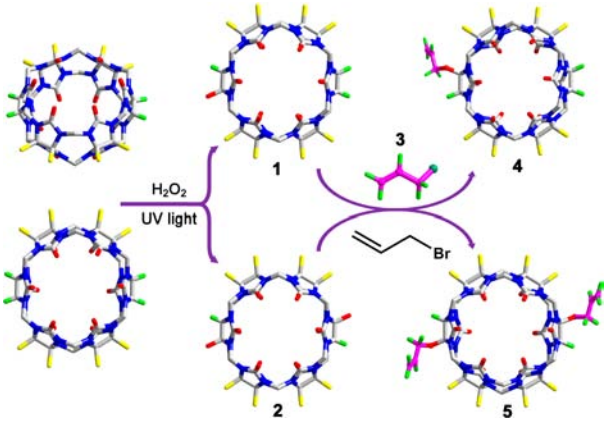


Figure 1. Synthesis of mono- and dihydroxylated octamethylcucurbituril (**1** and **2**) and their allylated products (**4** and **5**) with allyl bromide (**3**) from a symmetrical octamethylcucurbituril (OMeQ[6]).

Using the method published by Kim and co-workers,[21] alkyl-substituted cucurbit[*n*]urils (SQ[*n*]s) are easily decomposed by oxidation of persulfate salts, and almost no hydroxylated SQ[*n*]s were obtained in our laboratory, whereas using the method established by Bardelang and Ouari,[29,30] a mono-hydroxylated octamethylcucurbit[6]uril (**1**) and dihydroxylated octamethylcucurbit[6]uril mixture in which **2** as dominative dihydroxylated isomer (over 85%, see Figures S9 and S10 in the Supporting Information) were successfully obtained. The oxidation mixture, containing mainly OMeQ[6], (OH)-OMeQ[6], and $(OH)_2$OMeQ[6]s, could be readily separated on a silica gel column in the order $(OH)_2$OMeQ[6]s, (OH)OMeQ[6], and OMeQ[6]. There are no geometric isomers for (OH)OMeQ[6], three geometric isomers are possible for $(OH)_2$OMeQ[6]; two are mirror symmetrical with two hydroxyl groups at the same glycouril moiety (Figure 2a)

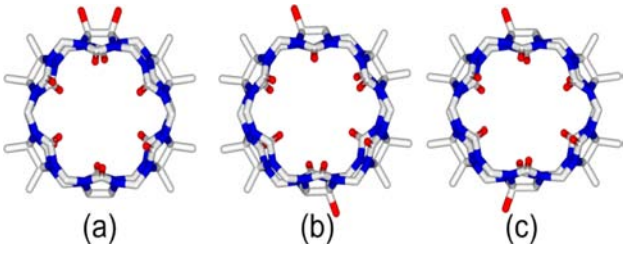


Figure 2. X-ray structures of three $(OH)_2$OMeQ[6] isomers: (a) with two hydroxyl groups at the same glycouril moiety; (b) central symmetrical, or *trans*-isomer; (c) with one hydroxyl group at opposite glycouril moieties, or *cis*-isomer.

and one hydroxyl group at opposite glycouril moieties (*cis*-isomer, Figure 2c), and one is central symmetrical (*trans*-isomer, Figure 2b). The dominative isomer **2** can be purified by recrystallizing dihydroxylated $(OH)_2$OMeQ[6] mixture with over 70% yield.

Figure 3a shows the ^{1}H NMR spectrum of **1**. There are four sets of methylene doublets at δ = 5.69, 5.66 (H1) and 4.29, 4.26 ppm (H9), δ = 5.61, 5.58 (H2) and 4.26, 4.23 ppm (H10), δ = 5.60, 5.56 (H3) and 4.36, 4.32 ppm (H8), δ = 5.43, 5.40 (H4) and 4.52, 4.48 ppm (H7), two methine singlets at δ = 5.44 ppm

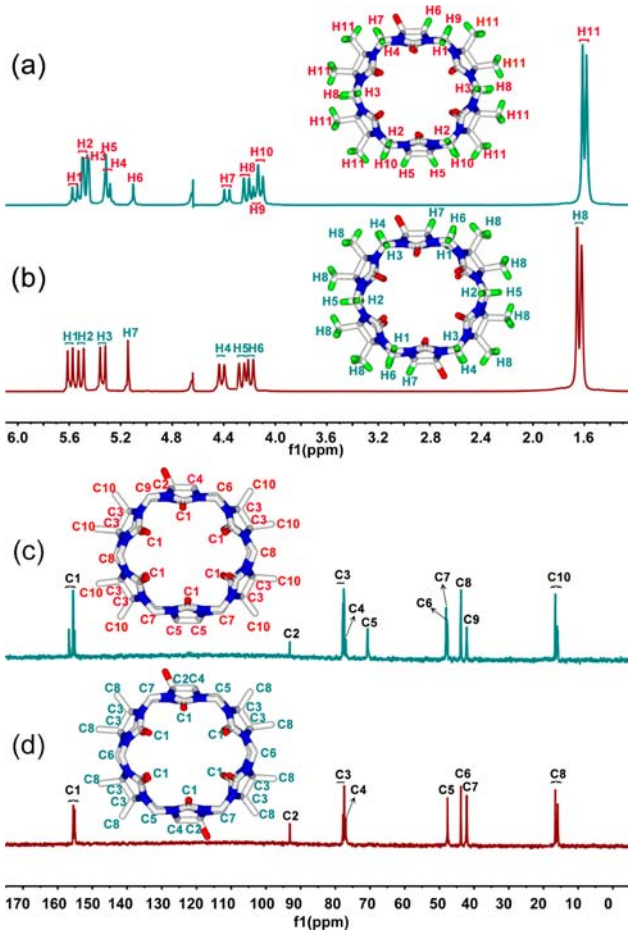


Figure 3. (a,b) ^{1}H NMR spectra of **1** and **2** in D_2O; (c,d) ^{13}C NMR spectra of **1** and **2** in D_2O.

(H5), one methine singlet close to the hydroxyl group at δ = 5.24 ppm (H6), and two methyl signals at δ = 1.73 and 1.70 ppm (H11), respectively. Detailed assignments were derived from gCOSY and ROESY spectra of **1** as shown in Figures S11 and S12 in the Supporting Information. Based on the assigned ^{1}H NMR and gHSQC 2D NMR spectra of **1** (Figure S13, Supporting Information), the ^{13}C NMR spectra of **1** was also assigned, which features four groups of resonances: carbonyl carbon resonances (C1) in the range δ = 155.15−156.74 ppm; methine group signals in the range δ = 93.13−70.71 ppm, with C2 at 93.13 ppm, C5 at 70.71 ppm, C4 at 77.03 ppm, and C3 in the range δ = 77.35−77.82 ppm; methylene group signals (C6−C9) in the range δ = 42.13−48.04 ppm, methyl group signals (C10) in the range δ = 15.90−16.62 ppm (Figure 3c). Figure 3b shows the ^{1}H NMR spectrum of **2** obtained by recrystallizing, in which there are three sets of doublets visible, suggesting **2** is not in the conformation shown in Figure 2c, which could contain four sets of doublets. A close inspection revealed that the proton (H7) near the hydroxyl groups was correlated with two neighboring methylene groups (H6, H4) in the ROESY spectrum (Figure S15, Supporting Information), suggesting **2** adopts the conformation shown in Figure 2b, because in the conformation shown in Figure 2a there could be only one correlation between the methine proton and neighboring methylene groups in the ROESY spectrum. Thus, it was relatively easy to assign the ^{1}H NMR spectrum of **2** as three sets of methylene doublets at δ = 5.63, 5.59 (H1)

DOI: 10.1021/acs.orglett.6b02789
Org. Lett. 2016, 18, 5544−5547

and 4.22, 4.18 ppm (H6), δ = 5.54, 5.50 (H2) and 4.29, 4.24 ppm (H5), δ = 5.37, 5.33 (H3) and 4.44, 4.40 ppm (H4), one methine singlet at δ = 5.15 ppm (H7), and two methyl signals at δ = 1.66 and 1.63 ppm (H8), respectively. Using the assigned ^{1}H NMR and gHSQC 2D NMR spectra of **2** (Figure S16, Supporting Information), the ^{13}C NMR spectra of **2** was also assigned, which features four groups of resonances: carbonyl carbon resonances (C1) in the range δ = 155.50−155.13 ppm; methine group signals in the range δ = 93.10−76.99 ppm, with C2 at 93.10 ppm, C3,4 at 77.03 ppm, C3 in the range δ = 77.78−76.99 ppm; methylene group signals (C5−C7) in the range δ = 47.67−42.12 ppm; methyl group signals (C8) in the range δ = 16.61−15.87 ppm (Figure 3d).

Xevo Q-TOF mass spectrometry of these two new hydroxylated SQ[6]s gave ions that were equivalent to (OH)OMeQ[6] and $(OH)_2$OMeQ[6] molecules (for the (OH)OMeQ[6] ion, for **1**·H·K$^+$: calcd. m/z 1165.1533, found m/z 1165.4052 and for the $(OH)_2$OMeQ[6] ion, for **2**·H·K$^+$: calcd. m/z 1181.1523, found m/z 1181.4122 as shown in Figures S17 and S18, Supporting Information).

Fortunately, we were able to determine the crystal structure of **1** in the presence of $MgCl_2$ and $CdCl_2$ in 3 M HCl solution, in which $[Cd_2Cl_8]^{4-}$ anions formed and functioned as a structure directing agent.[19,20,32] Moreover, we also obtained single crystals of **2** in neutral water in the absence of any metal salts. The crystal structure of **2** further confirmed our predicted structure for **2** (Figure 2b). The compound containing **1** is of the {**1**·$[Cd_2Cl_8]^{4-}$·4H_3O·6H_2O} type (**A**), while that containing **2** is of the {**2**·20H_2O} type (**B**). The X-ray diffraction data showed that when introducing Mg^{2+} and Cd^{2+} cations into the **1**-$MgCl_2$−$CdCl_2$−HCl system, molecule **1** did not coordinate with any metal ions, and a single hydroxyl group (O7) was shared between two positions for **1** (O7 and O7^a) with 50% occupancy, and this disorder is inherent to the OMeQ[6] structure owing to its symmetry (Figure 4a). Furthermore, the

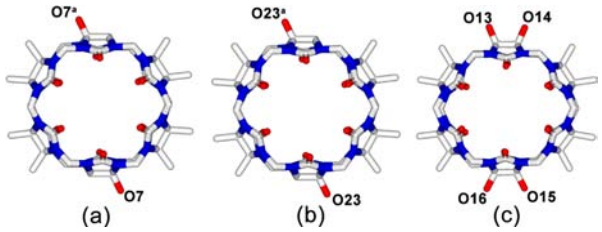


Figure 4. Crystal structures of (a) **1** with the OH group disordered over two positions in compound **A**, (b) **2** with two *trans*-OH groups with 100% occupancy, and (c) **2** with two *trans*-OH groups disordered over four positions in compound **B**.

Cd^{2+} cation formed $[Cd_2Cl_8]^{4-}$ anions in HCl solution, and these interact with six **1** molecules through the outer surface interaction of Q[n]s,[32] including ion-dipole interactions between chloride atoms from $[Cd_2Cl_8]^{4-}$ anions (Cl3 and C1) and carbonyl carbon atoms (C4, C10 and C7), respectively. Additionally, there exists hydrogen bonding between chloride atoms from $[Cd_2Cl_8]^{4-}$ anions (Cl1) and hydroxyl groups (O7) of **1** (Figure S19, Table S1, Supporting Information). The X-ray diffraction data revealed a simple crystal structure of **2** because nothing additional was introduced into the basic parent structure. There were two slightly different **2** molecules in compound **B**, one with two hydroxyl groups (O23 and O23^a) with 100% occupancy in the central symmetrical conformation, namely, the *trans*-conformation (Figure 4b), and another with two hydroxyl groups disordered over four positions, O13, O15 at *trans*-position with 60% occupancy, and O14, O16 at *trans*-position with 40% occupancy; Figure 4c). In order to identify the minor isomer in the dihydroxylated $(OH)_2$OMeQ[6] mixtures, a series of Ln^{3+} cation were introduced into solution containing $(OH)_2$OMeQ[6] mixture and a series of single crystals of $[Ln(H_2O)_x]^{3+}$/$(OH)_2$OMeQ[6] adducts with heavier lanthanide cations were obtained, respectively. Single crystal X-ray diffraction analysis showed that all crystals contained only *trans*-(OH)2OMeQ[6] isomer, except one with Yb^{3+}, in which $(OH)_2$OMeQ[6] could be *cis*-$(OH)_2$OMeQ[6] isomer (Table S2 and corresponding CCDC numbers of these compounds, Supporting Information).

Chemical modifications of the hydroxyl group on **1** and **2** were readily achieved through a Williamson reaction as shown in Figure 1. Compound **3** was reacted with hydroxyl group(s) to introduce single and double alkene group(s) onto the surface of **1** and **2**, respectively,[21,22] in particular, **2**, prepared for the first time, facilitates further functional reactions at two different positions simultaneously (Figure 1), providing a new route for introducing additional functionality or surface attachment of dihydroxylated Q[n]s. Referring to Scherman's method,[22] a bisethylimidazolium salt was used as a guest to make the host−guest inclusion complex, which rendered the normal Q[6]-based inclusion complex soluble in DMSO. However, in the present work, inclusion complexes of this guest with **1** and **2** could not be dissolved in DMSO. Thus, a *N*,*N*′-dihexyl viologen bromide salt (**6**) was selected to replace the bisethylimidazolium salt. Interestingly, **1** interacted with **6** to form a dumbbell-like inclusion complex in water, but formed a pseudorotaxane-like inclusion complex that was soluble in DMSO (Figure S20, Supporting Information). Thus, **1** in a 1:1 molar ratio of **1**:**6** reacted with **3** in the presence of sodium hydride to yield monoallylated OMeQ[6] (**4**). Figure 5a,b

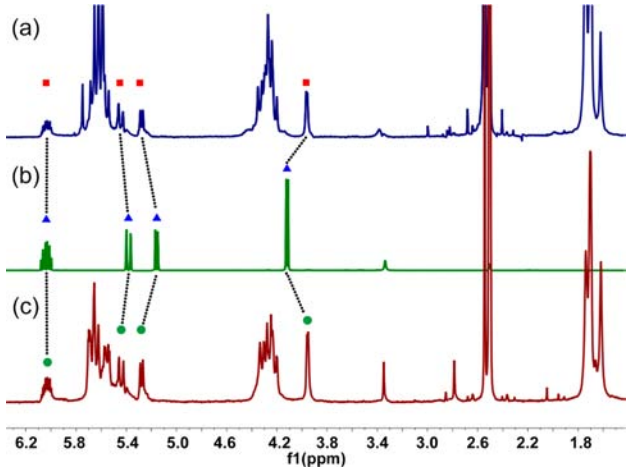


Figure 5. ^{1}H NMR spectra of (a) **4**, (b) **3**, and (c) **5** in DMSO-d_6.

shows a comparison of the ^{1}H NMR spectra of **4** and **3** in DMSO-d_6. A similar reaction process in which **2** in a 1:1 molar ratio of **2**/**6** reacted with **3** in the presence of sodium hydride yielded *trans*-diallylated OMeQ[6] (**5**), as shown in Figure 5c. ROESY spectra of **4** and **5** show the correlations of allyl and OMeQ[6] moieties (see Figures S21 and S22, Supporting Information). Xevo Q-TOF mass spectrometry gave ions that were equivalent to **4** and **5**, respectively (for **4**·2Na$^+$, calcd. m/z

DOI: 10.1021/acs.orglett.6b02789
Org. Lett. 2016, 18, 5544−5547

605.5, found m/z 605.2078(2) and for **5**·2Na$^+$, calcd. m/z 634.0, found m/z 633.2208(2), as shown in Figure S23 and S24, Supporting Information).

In summary, utilizing a moderate photochemical method to first introduce a limited alcohol function onto an alkyl-substituted cucurbit[n]uril, namely, OMeQ[6], we prepared two new mono- and dihydroxylated octamethylcucurbit[6]urils (**1** and **2**) using hydrogen peroxide and UV light. Separation of **1** and **2** using silicon gel 200−300 mesh provides a simple, reproducible and efficient method for controlled $(OH)_x$SQ[n] preparation. Regarding chemical modification, allylation could be readily carried out on the mono- and dihydroxylated hydroxyl group to provide the basis for single or double point(s) attachment on **1** and **2**. Unlike unsubstituted Q[n]s, which offer n different positions and could yield n dihydroxylated unsubstituted Q[n] isomers, OMeQ[6] offers only three positions for the dihydroxylated isomers, and only yields one preferred dihydroxylated isomer, namely, *trans*-isomer **2**. Thus, this could open up a new avenue for controlling the chemical modification of Q[n], especially larger Q[n]s or alkyl-substituted Q[n]s, to afford novel supramolecular assemblies for new applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02789.

General experimental procedures and analytical data for all new compounds (PDF)
X-ray data for compound **1** (**A**) (CIF)
X-ray data for compound **1** (**B**) (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the support of the National Natural Science Foundation of China (grant Nos. 21601090, 21272045, and 51463004).

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DOI: 10.1021/acs.orglett.6b02789
Org. Lett. 2016, 18, 5544−5547