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Opposing substitution in cucurbit[6]urils forms ellipsoid cavities: the symmetrical dicyclohexanocucurbit[6]uril is no exception highlighted by inclusion and exclusion complexes

Zheng Limei[a]; Zhu Jiannan[a]; Zhang Yunqian[a]; Zhu Qianjiang[a]; Xue Saifeng[a]; Tao Zhu[a]; Zhang Jianxin[b]; Zhou Xin[b]; Wei Zhanbin[c]; Long Lasheng[c]; Anthony I. Day[d]
[a] Institute of Applied Chemistry, Guizhou University, Guiyang, PR China [b] Key Laboratory of Chemistry for Natural Products of Guizhou Province, Guiyang, PR China [c] Department of Chemistry, Xiamen University, Xiamen, PR China [d] School of Physical, Environmental and Mathematical Sciences, University of New South Wales, Australian Defence Force Academy, Canberra, Australia

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Opposing substitution in cucurbit[6]urils forms ellipsoid cavities: the symmetrical dicyclohexanocucurbit[6]uril is no exception highlighted by inclusion and exclusion complexes

Zheng Limei[a], Zhu Jiannan[a], Zhang Yunqian[a], Zhu Qianjiang[a], Xue Saifeng[a], Tao Zhu[a1], Zhang Jianxin[b], Zhou Xin[b], Wei Zhanbin[c], Long Lasheng[c] and Anthony I. Day[d]*

[a]*Institute of Applied Chemistry, Guizhou University, Guiyang, PR China;* [b]*Key Laboratory of Chemistry for Natural Products of Guizhou Province, Guiyang, PR China;* [c]*Department of Chemistry, Xiamen University, Xiamen, PR China;* [d]*School of Physical, Environmental and Mathematical Sciences, University of New South Wales, Australian Defence Force Academy, Canberra, Australia*

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The symmetrical dicyclohexanocucurbit[6]uril has been synthesised by the controlled condensation of the diether of cyclohexanoglycoluril (1) and the dimer of glycoluril (2). The symmetrical dicyclohexanocucurbit[6]uril, $(CyH)_2Q[6]$, characterised by the ^1H NMR spectroscopy, ESMS and further confirmed by single crystal X-ray diffraction of a cobalt aqua exclusion complex, which demonstrates an ellipsoid cavity. Within a cucurbit[6]uril ellipsoid cavity, an inclusion complex of 5,5′-dimethyl-2,2′-bipyridine adopts a preferred orientation, aligning with the longest axis. The ellipsoid cavity is further supported by semiempirical AM1 gas phase calculations.

Keywords: symmetrical dicyclohexanocucurbit[6]uril; cucurbit[6]uril; inclusion complex; exclusion complex; bipyridine binding

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Introduction

Cucurbit[*n*]uril (Q[*n*]) (*1–5*) are a new family of molecular hosts that have aroused considerable interest in the area of supramolecular chemistry. Much of the host–guest chemistry of cucurbit[*n*]uril to date has focused on those unsubstituted homologues that have variable aqueous solubility in the presence of cations (*1–10*). Some effort has been made to introduce substitution in order to achieve ready solubility in both aqueous systems and common organic solvents (*11, 12*). As an ongoing part of our research efforts, we are developing methods for the introduction of substitution for the purpose of solubility manipulation, as well as the study of the effects of these substituents upon the binding of a molecular guest. Our key goals are to introduce substitution in a controlled manner and to explore the variety of possible substitutions. Substituted and unsubstituted Q[*n*] have potential applications in many areas including separation and purification technologies (*8*), analytical and sensors devices (*11*) and drug delivery (*7*).

Since, the discovery of the first fully substituted Q[*n*], decamethylcucurbit[5]uril, $Me_{10}Q[5]$ in 1992 (*13*), there were no reports of substituted Q[*n*] for almost a decade. Recently, a number of fully and partially substituted Q[*n*] have been reported. These include the fully substituted (cyclohexano, CyH) $(CyH)_5Q[5]$ and $(CyH)_6Q[6]$ (*11*), $Me_{12}Q[6]$ (*14*) and $(HO)_{2n}Q[n]$ (*15*), and the partially substituted $Ph_2Q[6]$ (*16*), $Me_6Q[6]$ (*12*), $Me_4Q[6]$ (*17*), and $(Me_2CyP)_nQ[6]$ (*14*). In addition, there has been one report of substituted cucurbituril analogues (*18*). While achieving organic solubility, the fully substituted Q[*n*] suffer the limitation that Q[5] is always the major product and that overall yields are lower. Partial substitution, on the other hand, avoids these problems and also precludes the need for large quantities of potentially difficult to obtain or expensive substituted glycolurils.

We first demonstrated the controlled synthesis of the symmetrical $Me_4Q[6]$ (*17*) utilising the readily available dimer of glycoluril (**2**) (*19*), and now report the extension of this method to introduce a cyclic substitution group. Condensing the diether of cyclohexanoglycoluril (**1**) with the glycoluril dimer (**2**) produces a new symmetrically substituted Q[*n*], α,δ-dicyclohexanocucurbit[6]uril (α,δ-$(CyH)_2Q[6]$; Scheme 1) [2], in a controlled manner. α,δ-$(CyH)_2Q[6]$ shows good water solubility, which allowed us to investigate the structure and compare the host–guest binding properties of this new substituted Q[*n*] with those of α,δ-$Me_4Q[6]$ (*17*).

Experimental

5,5′-Dimethyl-2,2′-bipyridine was obtained from Aldrich and used without any further purification. The corresponding HCl salt of 5,5′-dimethyl-2,2′-bipyridine was prepared by

*Corresponding author. Email: a.day@adfa.edu.au

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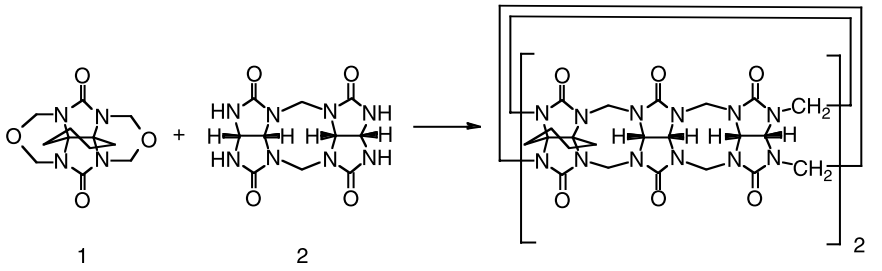

Scheme 1.

dissolving bipyridine in concentrated HCl followed by precipitation with ethanol, filtered and then dried.

Both the ^{1}H NMR and ^{13}C NMR spectra were recorded at 20°C on a VARIAN INOVA-400 spectrometer as solutions in D_2O at 400 and 80 MHz, respectively. ESMS spectra were recorded on an HP 1100 LC–MSD, and molecular modelling was carried out using HyperChem 7.5 (*20*).

*Synthesis of 1,6:3,4-bis(2-oxapropylen)tetrahydro-3***a***,6***a***-butano-imidazo[4,5-***d***]imidazol-2,5 (1***H***,3***H***)-dione (1)*

Cyclohexanoglycoluril (*21*) (25.1 g, 20 mmol), formaldehyde (37%, 60 ml), H_2O (30 ml) and concentrated HCl (100 ml) were stirred together at room temperature for 3 h. The resultant precipitate was collected by filtration, washed with water and dried to obtain the diether (**1**) (yield: 22.0 g, 61%). The ^{1}H NMR spectrum was identical to that reported previously (*22*), but the yield has been doubled with our shorter reaction times.

Synthesis of the symmetrical dicyclohexanocucurbit[6]uril

The diether of cyclohexanoglycoluril (**1**) (2.8 g, 10 mmol), the dimer of glycoluril (**2**) (*19*) (4.16 g, 13.5 mmol), potassium chloride (0.97 g, 13.5 mmol) and concentrated HCl (25 ml) were stirred together and heated under reflux for 1 h. The resultant dark red solution was cooled to room temperature and KCl crystals formed. The crystals (KCl) were removed by filtration and the HCl removed *in vacuo*. Water (200 ml) and acetone (100 ml) were added to the residue and the precipitate collected by filtration, washed with acetone and then dried to give a reddish solid. The ^{1}H NMR spectrum of the crude reaction mixture revealed that the reddish solid contained α,δ-$(CyH)_2$Q[6] (Figure 1) as the major product, together with small amounts of unidentified substituted products and homologues. Recrystallisation of the crude product from 3 M HCl produced colourless crystals (yield: 3.5 g, 30%); m.p. dec >293°C; ν_{max} KBr: 1731, 1481, 1327, 1240, 1197, 804 cm^{-1}; ^{1}H NMR (Figure 2); ^{13}C NMR: 13.7 (CH_2 cyclohexane ring), 23.3 (CH_2 cyclohexane ring), 46.9 (CH_2) 50.1 (CH_2), 69.1 (CH), 76.8 (qC), 156.6 (CO); ESMS: *m/z* 1143.2 (see Discussion section).

X-ray

Syntheses of the single crystals of α,δ-$(CyH)_2$Q[6] $Co(NO_3)_2$ adduct were obtained by dissolving α,δ-$(CyH)_2$Q[6] in a solution of $Co(NO_3)_2{\cdot}6H_2O$ in H_2O. The final solution was mixed thoroughly and allowed to stand at room temperature. Light pink crystals were formed after several days. All experiments were carried out under air.

The structure of the $Co(NO_3)_2$ adduct of α,δ-$(CyH)_2$Q[6] was determined by single crystal X-ray diffraction on a CCD Smart diffractometer. The α,δ-$(CyH)_2$Q[6] $Co(NO_3)_2$ structure is well-defined, while

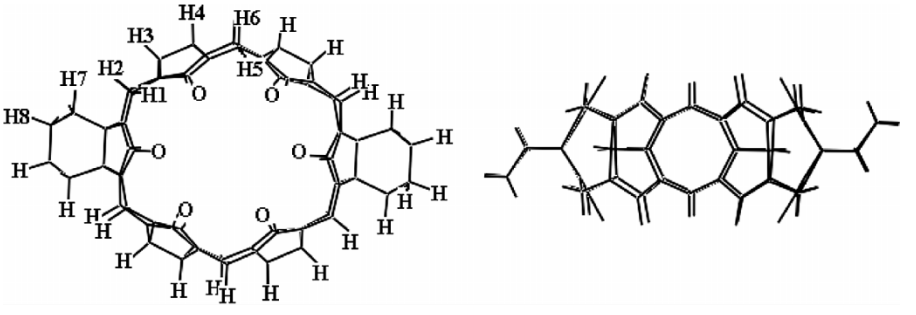

Figure 1. On the left is the structure of α,δ-$(CyH)_2$Q[6], as viewed from above a portal, and on the right, as viewed from the side.

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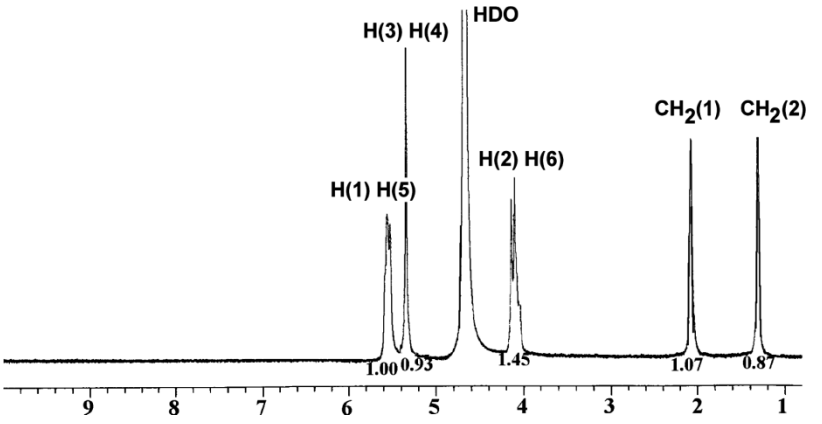

Figure 2. The ^{1}H NMR spectrum of α,δ-$(CyH)_2$Q[6] in D_2O.

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many of the water molecules within the crystal are in a state of disorder. The disordered water was not refined. Crystallographic data for structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as a Supplementary Publication No. CCDC 640109.

Results and discussion

^{1}H NMR spectroscopy of α,δ-$(CyH)_2$Q[6] and its inclusion complex of 5,5′-dimethyl-2,2′-bipyridine·HCl

Cucurbituril α,δ-$(CyH)_2$Q[6] has been fully characterised by the ^{1}H NMR spectroscopy, ESMS and X-ray diffraction. The most significant feature of α,δ-$(CyH)_2$Q[6] is its D_{2h} symmetry, which results in a relatively simple ^{1}H NMR spectrum (Figure 2). The proton resonances for H(2), H(6) and H(1), H(5) appear as two multiplets centred at 4.09 and 5.53 ppm, respectively, but do not appear as two clearly defined sets of doublets as could be expected. The methine proton resonances are found at 5.33 ppm as a singlet, and the remaining resonances at 2.07 and 1.30 ppm are consistent with the methylene protons of the cyclohexane ring. Analysis by ESMS supported the structure of α,δ-$(CyH)_2$Q[6] with molecular ions, such as *m/z* 1143.2, [α,δ-$(CyH)_2$Q[6] $+K^+$]; *m/z* 1217.2, [α,δ-$(CyH)_2$Q[6]+($K2Cl)^+$]; *m/z* 591.2, 1/2[α,δ-$(CyH)_2$Q[6]+$2K^+$]; *m/z* 575.3, 1/2[α,δ-$(CyH)_2$Q[6]+$2Na^+$]; *m/z* 583.3, 1/2[α,δ-$(CyH)_2$Q[6] + Na^+ + K^+], consistent with the parent α,δ-$(CyH)_2$Q[6] coordinating K^+ or Na^+ ions (*2a*).

There were few indicators in the ^{1}H NMR spectrum, which could be used to clearly define the structural features of α,δ-$(CyH)_2$Q[6], until we examined the binding of the HCl salt of 5,5′-dimethyl-2,2′-bipyridine, dmbpy·HCl in this new substituted Q[6]. A stable 1:1 inclusion complex of dmbpy·HCl@α,δ-$(CyH)_2$Q[6] was formed, which clearly resolved the structural features of α,δ-$(CyH)_2$Q[6] through peak separations as a consequence of the shielding effects of the pyridine rings and the formation of an unsymmetrical complex (Figure 3). We had previously found similar peak separation effects for the inclusion complex of bipyridine·HCl and the symmetrical Me_4Q[6] (*17*).

Notably, all the resonances for the methylene protons of dmbpy·HCl@α,δ-$(CyH)_2$Q[6] are clearly distinguishable as sets of doublets at 3.60, 3.87, 4.17, 4.88, 5.48, 5.60 and 5.62 ppm. In addition, the methine proton resonances occur as doublets at 5.00 and 5.20 ppm (Figure 4(b)). There are a number of reasons for the separation of peaks. These include the shielding effects of the pyridine rings, the unsymmetrical nature of the complex and an apparent preferred orientation of the guest within the cavity. The loss of symmetry in the complex is indicated by two sets of resonances for the dmbpy·HCl guest giving a total of eight pyridine proton resonances. These resonances are shifted in both magnetic field directions compared to the uncomplexed dmbpy·HCl salt (Figure 4(a)).

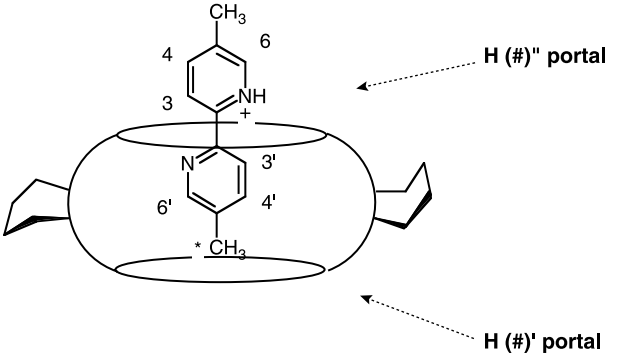

Figure 3. A structural representation of the dmbpy·HCl@α,δ-$(CyH)_2$Q[6] complex, indicating both the extent of encapsulation and the orientation of the guest relative to the cyclohexano substituents. The two portals are magnetically different (protons indicated H(#)″ and H(#)′) as a result of the unsymmetrical insertion of the guest.

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The proton resonances of one of the pyridine rings are shifted upfield by 0.2–1.1 ppm (cavity-bound pyridine protons: 1.75, CH_3*; 6.67, H(4)*; 7.39, H(3)*; 7.56, H(6)*) indicating a deep cavity complex. The proton resonances of the second ring are shifted downfield by 0.2–0.3 ppm (portal-bound pyridine protons: 2.46, CH_3; 8.25, H(4); 8.40, H(6); 8.69, H(3)), indicating that the second pyridine ring is near or just outside the portal of the Q (*2d, 5*). The consequent effect upon the Q proton resonances is that the methylene resonances near one portal are magnetically non-equivalent to those near the opposite portal. This is clearly evident from the large difference in separation between the methylene proton resonances H(5)′, H(5)″, H(6)′ and H(6)″ (5.48, 4.88, 3.87 and 3.60 ppm, respectively). H(1)′ and H(1)″ are only slightly shifted, while H(2)′ and H(2)″ are not affected (5.62, 5.60, 4.17 and 4.17 ppm, respectively). The large upfield chemical shifts for H(5)′, H(5)″, H(6)′ and H(6)″ are also a clear indication of a preferred orientation of the guest, dmbpy·HCl, where the face of the pyridine ring imposes a magnetic effect upon these protons. The largest effect is found for H(5)″, indicating that this proton is closest to the centre of the pyridine ring. This observation indicates that the methylene proton is angled inwards towards the portal opening (i.e. nearest to the portal axis). Furthermore, H(5)″ and H(6)″ are the methylene protons situated at the greatest distance from the glycoluril moiety carrying the cyclohexano substituent and, hence, suggests a preferred orientation of the guest within the cavity (Figure 5). This is also supported by the fact that H(1)′ and H(1)″ are only slightly affected and that H(2)′ and H(2)″ are not affected. These methylene protons are the closest linking groups to the cyclohexanoglycoluril moieties. The preferred orientation is also reflected in a chemical shift difference between the methine protons H(3) and H(4) at 5.20 and 5.00 ppm, respectively, which appear as doublets (7.5 Hz).

By comparison, the relative chemical shifts observed for the proton resonances of the dmbpy·HCl guest bound in unsubstituted Q[6] (Figure 6) are similar in direction and are only slightly variable in magnitude. The largest differences (0.09 ppm further upfield) are found for the dmbpy·HCl guest protons, and H(6)′ and H(4)′ when the guest is bound in the cavity of α,δ-$(CyH)_2$Q[6] compared to unsubsituted Q[6]. What is particularly striking here is the difference in the magnitudes of the chemical shifts of the magnetically non-equivalent methylene protons. The Q methylene proton resonances of the association complex dmbpy·HCl@Q[6] (Figure 6) appear as two sets of doublets at 4.04, 4.11, 5.43 and 5.65 ppm as a consequence of the formation of an unsymmetrical association complex and shielding of the methylene protons nearest to the centre of the pyridine ring, a

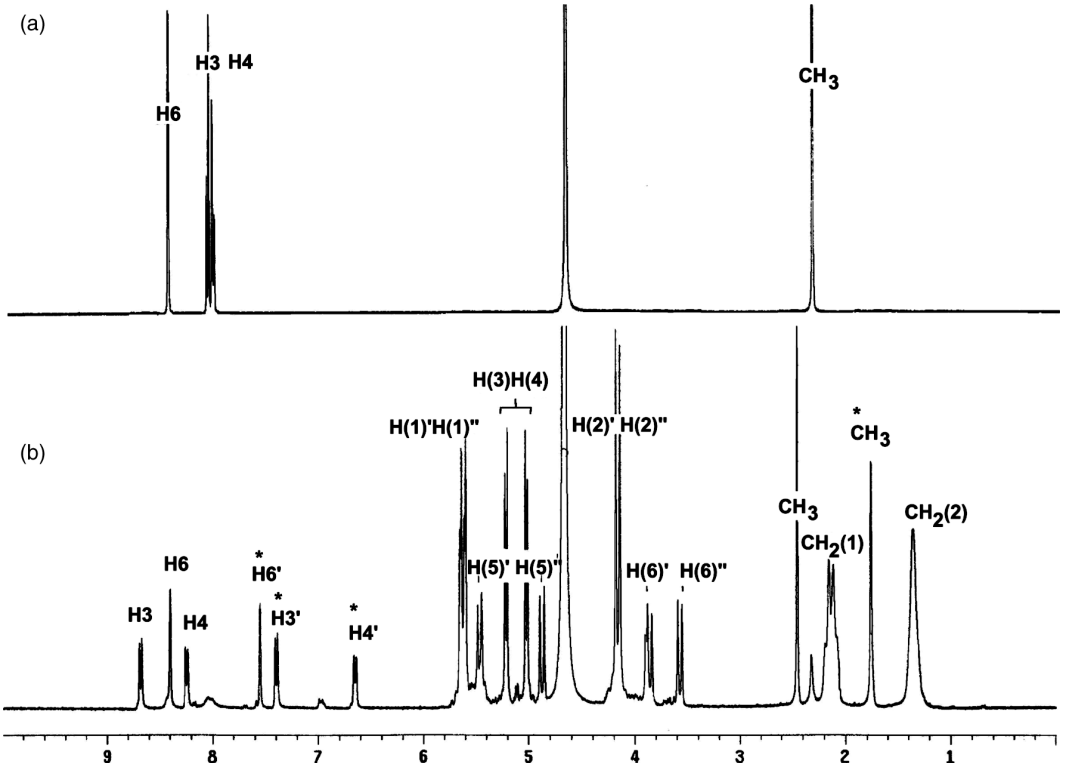

Figure 4. (a) The ^{1}H NMR spectrum of dmbpy·HCl in D_2O. (b) The ^{1}H NMR spectrum of dmbpy·HCl@α,δ-$(CyH)_2$Q[6] in D_2O. The guest proton resonances are shown without parentheses, and the cavity-bound proton resonances are indicated by asterisks.

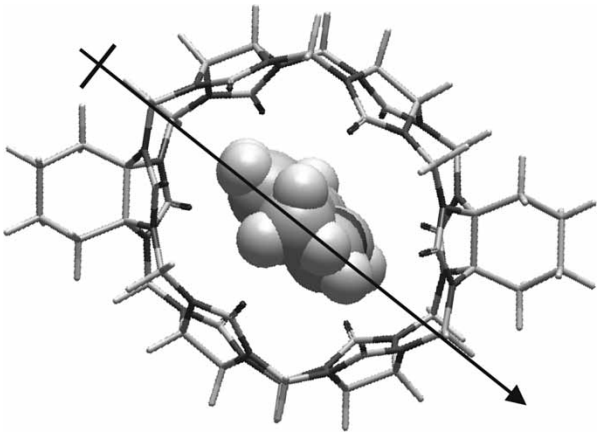

Figure 5. A molecular model of dmbpy·HCl@ α,δ-$(CyH)_2$Q[6] showing the preferred orientation of the dmbpy·HCl guest, which corresponds to the plane of the longest axis (arrow) of the ellipsoid cavity.

similar finding to that previously reported for bpy·HCl@Q[6] (*23*). The most significant feature found with α,δ-$(CyH)_2$Q[6] was the relative upfield chemical shifts of the methylene protons of the Q portal of α,δ-$(CyH)_2$Q[6], H(5)″ and H(6)″ affected by the protruding guest (Figure 3) compared to the same guest-affected portal protons, H(a)″ and H(b)″ of unsubstituted Q[6] (difference of 0.69, 0.47, 0.13 and 0.09 ppm upfield, respectively, relative to no guest present). The larger upfield shifts of the H(5)″ and H(6)″ proton resonances, compared to the H(a)″ and H(b)″ resonances, further supports the guest with a preferred orientation in an ellipsoid cavity. A larger chemical shift occurs as a result of the closer proximity of the guest to the methylene protons and a reduction in chemical shift averaging as a consequence of a preferred orientation.

Also, a ROESY NMR spectrum showed relatively strong host–guest cross-correlation peaks between the H(4)′ proton on the cavity-bound ring of dmbpy·HCl and the methine H(3) and H(4) protons of α,δ-$(CyH)_2$Q[6]. This again is consistent with a preferred orientation of the guest in an ellipsoid cavity (supporting information).

Semiempirical AM1 gas phase calculations confirm a preferred orientation of the dmbpy·HCl guest in an ellipsoid cavity of α,δ-$(CyH)_2$Q[6] (Figure 5). The cross-portal distances between carbonyl *O* (atom centre to atom centre) are ~7.05 Å at the greatest distance and ~5.85 Å at the remaining shorter ellipsoid distance. In solution and in the absence of a guest in α,δ-$(CyH)_2$Q[6], an ellipsoid cavity is not obvious from its ^{1}H NMR spectrum (Figure 2). However, semiempirical calculations performed in the absence of a guest indicated that an ellipsoid cavity is the optimal shape, with the substituted glycoluril moieties situated near the points of the longest dimension of the ellipse. We previously reported the crystal structure of α,α′,δ,δ′-Me_4Q[6] without a guest (*17*), where we also found that the cavity of this Q was not circular but ellipsoid.

The crystal structure of α,δ-$(CyH)_2$Q[6] as a $Co(NO_3)_2$ adduct also shows an ellipsoid cavity. However, unlike the structure of α,α′,δ,δ′-Me_4Q[6], which was determined in the absence of coordinating metals, the structure of α,δ-$(CyH)_2$Q[6] which we report here is complexed as a Co^{2+} aqua adduct. This prevents the unambiguous conclusion that its ellipsoid

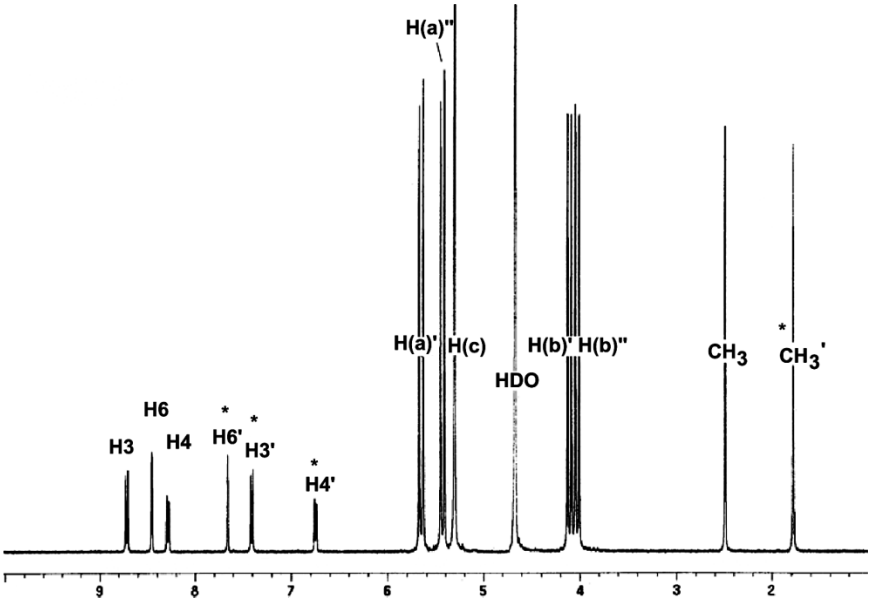

Figure 6. The ^{1}H NMR spectrum in D_2O of dmbpy·HCl bound in unsubstituted Q[6]. The two portals are magnetically different; hence the methylene protons H(a) and H(b) give two sets of doublets.

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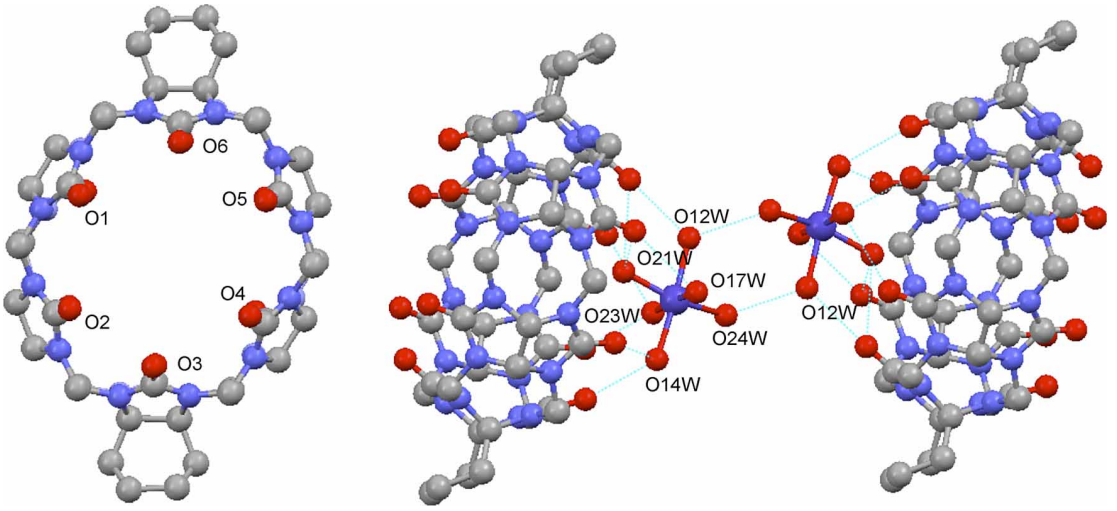

Figure 7. Crystal structure of α,δ-$(CyH)_2$Q[6]Co^{2+} aqua$(NO_3)_2$ adduct showing the relative relationship of the α,δ-$(CyH)_2$Q[6] to Co^{2+} metal centres (side view). The acetate and uncomplexed water molecules have been omitted for clarity. The LH structure is a portal view showing only α,δ-$(CyH)_2$Q[6].

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structure is a consequence of the bond angle constraints of the substituted glycoluril moieties imposed on the Q molecular framework and not the influence of the Co^{2+} aqua. However, as has been discussed, modelling would suggest that the ellipsoid cavity is independent of the coordinating metal, in solution or in the solid state.

Crystal structure of $Co(NO_3)_2$ adducts with α,δ-$(CyH)_2$Q[6]

The pale pink crystals of the $Co(NO_3)_2$ adduct of α,δ-$(CyH)_2$Q[6] were found to be very stable in air. It has been our experience that various crystals of Q[*n*] lose solvent of crystallisation leading to a deterioration of their crystalline integrity, but this was not observed for the $Co(NO_3)_2$ adduct of α,δ-$(CyH)_2$Q[6]. Single crystal X-ray diffraction determination revealed the structure of α,δ-$(CyH)_2$Q[6] complexed at the portals in the second coordination sphere through hydrogen bonding of water molecules in the first coordination sphere of Co^{2+}. The cavity is again ellipsoid, as was found with the α,α′,δ,δ′-Me_4Q[6] (*17*).

The elliptical portal has dimensions of ~7.2 Å at the longest points between O4–O5 and O6–O2. The shortest cross-portal carbonyl *O* distance is ~6.6 Å (O3–O1; Figure 7). This solid-state finding supports the solution ^{1}H NMR results found for the guest binding of dmbpy·HCl in α,δ-$(CyH)_2$Q[6], which indicates an ellipsoid cavity. Notably, an ellipsoid cavity would more readily accommodate a pyridine ring than a circular cavity. The benzene ring of *p*-$NH_3^+CH_2C_6H_4CH_2NH_3^+$ in unsubstituted Q[6] is known through crystal structures to distort the cavity into an ellipsoid shape (*25*).

The Co^{2+} ions are coordinated directly to six H_2O for each metal centre. Some of the Co^{2+} aqua complexes interact with the portals of α,δ-$(CyH)_2$Q[6] to form a one-dimensional supramolecular assembly in the solid state, in which the cucurbituril molecules stack on top of one another through O–O (2.792–3.005 Å) (O12w–O24w, O12w–O18w, O18w–O17w, O18w–O23w), interactions between two adjacent metals. Supramolecular chains form layers in the *XZ*-plane. The interchain space is filled with nitrate anions and water molecules that form a complicated interconnecting hydrogen bonding network. The hydrogen bonding interaction of the Co^{2+} aqua complex of three H_2O hydrogen bonded to the portal is also found in the smallest arc of the elliptical arrangement of the portal O.

The crystal system of α,δ-$(CyH)_2$Q[6] (referring to Figure 7) belongs to a triclinic system with space group $P-1$. The crystal parameters are as follows: $a = 12.583(2)$ nm, $b = 14.793(2)$ nm, $c = 27.829(4)$ nm, $\alpha = 104.991(3)°$, $\beta = 90.060(3)°$, $\gamma = 114.157(3)°$, $V = 4532.0(12)$ Å^3, $D_c = 1.653$ g/cm^3, $Z = 1$, $F_{000} = 2368$, $R1 = 0.1376$ ($I > 2\sigma(I)$), $Rw = 0.3899$. See supporting information for the data of non-hydrogen atomic coordinates, equivalent isotropic thermal parameters, bond lengths and angles.

Conclusion

The formation of an ellipsoid cavity in both α,δ-$(CyH)_2$Q[6] and α,α′,δ,δ′-Me_4Q[6] implies that the substituted glycoluril favours more acute angles (or tighter arcs) of the methylene-linked ureide N than unsubstituted glycolurils. This helps to explain the

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propensity for substituted glycolurils to condense with formaldehyde in producing predominantly the smaller Q homologues when all the glycoluril units are substituted (*11*, *14*). In addition, this is a significant controlling factor in the synthesis of partially substituted Q[*n*] (*12, 14, 17*). This finding has ramifications when considering the synthesis of fully substituted and partially substituted Q[*n*] and the selection of a suitably substituted glycoluril in order to obtain homologues as a complete family rather than being limited to the smaller homologues. The building block method described in this paper utilises the unsubstituted dimer of glycoluril (**2**) and the diether of a substituted glycoluril to effect a controlled introduction of substitution into Q[6]. While the isolated yield of α,δ-$(CyH)_2$Q[6] was modest, the crude ^{1}H NMR spectrum indicated that the yield was much higher than that isolated. It is clear that the introduction of cyclohexanoglycolurils into Q limits the homologue set to the smallest Q[5–6]. However, the synthesis of substituted Q[6] via a controlled introduction of the substituent opens the way to more elaborate Q[6] structures that are likely to present surprising physical properties, in particular host–guest binding. As has become apparent from the synthesis of α,δ-$(CyH)_2$Q[6] and our previously synthesised symmetrical Me_4Q[6] (*17*), the effect of introducing substituents is not benign as we have found two significant changes. These, in the example presented, are that the shape of the Q cavity is changed, and the host–guest binding interaction has changed. The preferred orientation of the dmbpy·HCl salt is an indicator of future binding differences which may provide features that can be manipulated to advantage. It could be expected that an ellipsoid cavity would improve van der Waals contacts by virtue of a better fit for flatter molecular guests such as the aromatics, but so far such advantages can only be a speculation. From the ^{1}H NMR, it is found that there is no discernable difference in the binding constants for dmbpy·HCl@-α,δ-$(CyH)_2$Q[6] compared to unsubstituted Q[6], as the binding constants are high for both. Binding differences might be expected in the discrimination or molecular recognition of guests, related to the shape of a potential guest but this has yet to be tested.

We are currently exploring the application of glycolurils that favour a flatter arc and more complex systems in order to determine applicable limits to this method of introducing substitution into Q[6–8].

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Notes

1. Email: gzutao@263.net
2. As a simple method of identifying the position of substitution within a Q[*n*] we propose the use of a Greek letter prefix to the name, e.g. α,δ-dicyclohexanocucurbit [6]uril, α,δ-$(CyH)_2$Q[6], where a Greek letter in alphabetical order, designates the position of each substituted glycoluril within a homologue.

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