Encapsulation of the haloalkane 4-chloromethylpyridine hydrochloride by cucurbit[8]uril

Pei-Hui Shan,[a] Yun Lu,[a] Zhi-chao Yu,[a] Ying Fan,[a] An-ting Zhao,[a] Carl Redshaw,[b] Zhu Tao,[a] and Xin Xiao,*[a]

Abstract: Complexation of 4-chloromethylpyridine hydrochloride (G) with cucurbit[8]uril (Q[8]) has been investigated using NMR spectroscopy, UV-visible spectroscopy, isothermal titration calorimetry (ITC), and X-ray crystallography. The data indicated that the guest 4-chloromethylpyridine hydrochloride is completely encapsulated by the cavity of the Q[8] host in both aqueous solution and the solid state, generating a highly stable inclusion complex, namely G_2@Q[8]. Interestingly, ion–dipole interactions and hydrogen-bonding interactions play a central role in the formation of the inclusion complex G_2@Q[8], which provides a reliable basis for the encapsulation of small organic guests by the hydrophobic microenvironment of the cavity.

Introduction

Macrocyclic host molecules, which are organic molecules possessing a strict structure and a specific confined space, such as hydrophobic cavities can provide a microenvironment for organic reactions. [1-3] Therefore, they are also widely used in the field of supramolecular catalysis. Over the past decade, it has been well established that organic molecules and ions can experience encapsulation in the cavity of the host, with the macrocyclic hosts cyclodextrins, calixarenes, cucurbiturils and pillararenes receiving much interest.[4-15] On the other hand, 4-chloromethylpyridine hydrochloride plays an important role in chemical synthesis, and can be used to produce various pesticides, pharmaceutical intermediates, insecticides, herbicides and fungicides.[16-18] Interestingly, 4-chloromethylpyridine has two active sites, namely the haloalkane and pyridyl moieties. This prompted us to wonder what kind of behavior would occur when 4-chloromethylpyridine is encapsulated within the microenvironment of a hydrophobic cavity. Therefore, we consider the recognition and encapsulation of 4-chloromethylpyridine hydrochloride to be an important study in supramolecular chemistry. It is therefore necessary to investigate which macrocyclic host molecules can interact with 4-chloromethylpyridine hydrochloride.

Cucurbit[*n*]urils (abbreviated as Q[*n*]s, n = 5–8, 10, 13–15) [19-25] have recently been added to the macrocyclic family in supramolecular chemistry, and are composed of n glycoluril units linked by 2n methylene groups. They contain not only hydrophobic cavities but also carbonyl-laced portals, and the presence of the former allows for the encapsulation of some guest molecules of appropriate size. [26-35] For example, Q[8] has been widely studied given its larger cavity, *versus* Q[6] and Q[7], which means it can better encapsulate various guest molecules of different sizes. In the current contribution, we have examined the binding properties of Q[8] with 4-chloromethylpyridine hydrochloride (G), using NMR spectroscopy, UV-visible spectroscopy, isothermal titration calorimetry (ITC), and X-ray crystallography. The results indicate the formation of a 1:2 host-guest inclusion complex, both in aqueous solution and in the solid state.

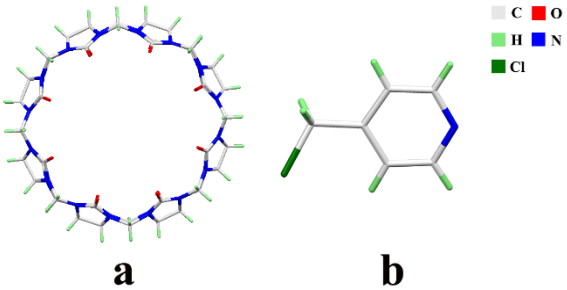

Figure 1. Structure of (a) the cucurbit[8]uril and (b) the guest 4-chloromethylpyridine hydrochloride.

Results and Discussion

NMR spectroscopy.

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In order to investigate the solution complexation of Q[8] with G, we initially performed ^{1}H NMR spectroscopic titration experiments by adding increasing amounts of Q[8] to G in D_2O. The ^{1}H NMR titration spectra of guest G were recorded both in the absence, and in the presence of various equivalents of the host Q[8] in aqueous solution, and the spectral data are collected in Figure 2. As shown in Figure 2, in the presence of Q[8], all the proton resonances associated with bound G experience upfield shifts. For example, the protons Ha and Hb undergo upfield shifts of 0.30 ppm and 0.74 ppm, respectively. Moreover, the proton Hc also experiences an upfield shift. In summary, based on the ^{1}H NMR spectra, we can conclude that the guest is encapsulated within the Q[8] cavity, thereby generating a host–guest inclusion complex.

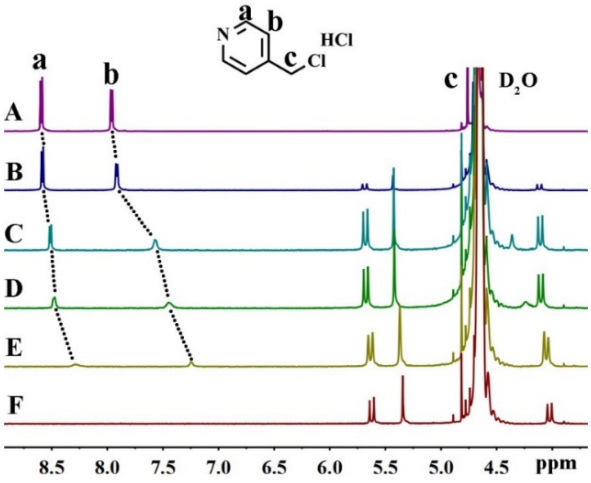

Figure 2. ^{1}H NMR spectra of G (2.0 mmol/L) in the absence (A) and presence of 0.25 (B), 0.52 (C), 0.73 (D), 1.02 (E) equiv. of Q[8] and (F) neat Q[8] (1.0 mmol/L) in D_2O at 20ºC.

UV/vis absorption and fluorescence emission spectra.

The binding interaction of Q[8] toward G in aqueous solution was next investigated using UV-vis spectroscopic titration experiments. As shown in Figure 3a, guest G exhibits characteristic absorption peaks at 230 nm, and with the gradual addition of Q[8], the absorbance intensity of G dramatically decreases, indicative of the binding affinity of Q[8] toward G. Furthermore, using the mol ratio method (Figure 3b), the binding interaction of Q[8] with G was fitted to a 1:2 (host : guest) binding model. Moreover, a continuous variation Job's plot (Figure 4) further confirmed that the Q[8]/G inclusion complex is formed with a 1 : 2 stoichiometry.

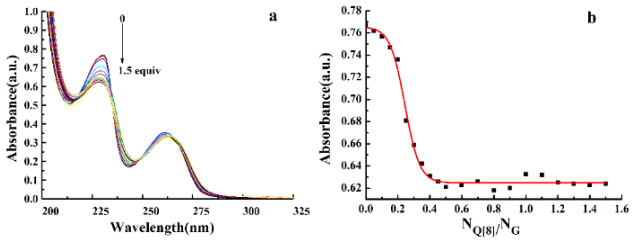

Figure 3. (a) UV-vis titration of G (8×10^{-5} mol·L^{-1}) on increasing concentrations of Q[8] and (b) absorbance (A) *vs.* the ratio of the number of mol of host and guest $N_{Q[8]}/N_G$.

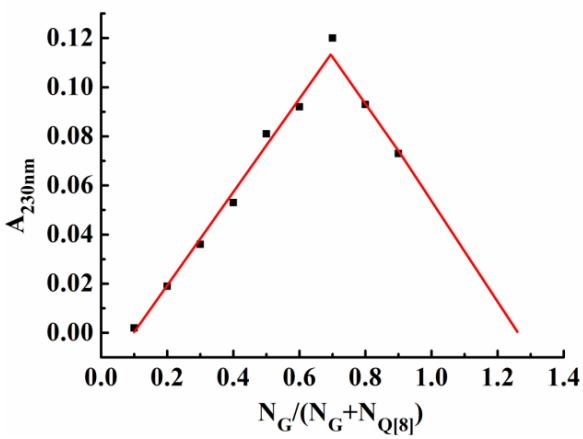

Figure 4. Continuous variation Job's plot for Q[8] and the guest on the basis of UV-vis titration spectra.

Isothermal titration calorimetry.

Quantitative data on the host–guest complexation of this system was obtained via isothermal titration calorimetry (ITC) experiments (Figure 5). The overall binding constant (K_a) for the complexation of the 4-chloromethylpyridine hydrochloride guest with the Q[8] host was calculated at 3.602×10^{11} M^{-2}. In addition, the relatively large negative enthalpy values observed for this system indicated that a favorable enthalpy change was the main driver toward the formation of the inclusion complex between Q[8] and 4-chloromethylpyridine hydrochloride (Table 1).

Figure 5. ITC profile of host Q[8] with guest G at 298.15 K.

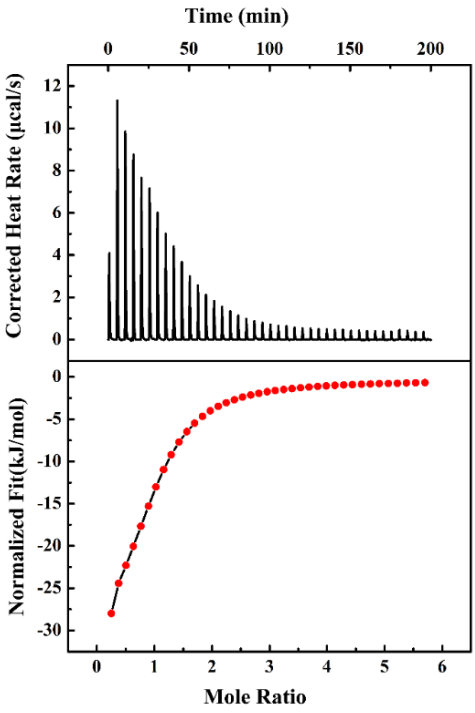

Table 1. Thermodynamic parameters obtained by ITC for the complexation in aqueous media at 25 °C.

Experiment	G_2@Q[8]
K_a (M^{-2})	3.60×10^{11}
K_{a1} (M^{-1})	$(8.82\pm0.92)\times10^{7}$
K_{a2} (M^{-1})	$(4.08\pm0.01)\times10^{4}$
ΔH1 (kJ·mol^{-1})	-200.00±8.27
ΔH2 (kJ·mol^{-1})	-34.04±0.04
TΔS1 (kJ·mo^{l-1})	-154.65
TΔS2 (kJ·mol^{-1})	-6.83

Crystal structure of complex 1

The binding behavior of Q[8] with the guest 4-chloromethylpyridine hydrochloride in the solid-state was investigated using X-ray diffraction. Numerous attempts were made to form suitable crystalline samples, and herein we present the crystal structure of the host-guest complex **1**, namely $[(C_{48}H_{48}N_{32}O_{16})\ @2(C_6H_7NCl)^+]\cdot16(H_2O)\cdot2Cl^-$. The single-crystal structure determination reveals that complex **1** crystallizes in the monoclinic crystal system, with the chiral space group $P2_1/c$. As shown in Figure 6, the guest 4-chloromethylpyridine hydrochloride is fully encapsulated by the cavity of the Q[8] host, and this is in accord with what we have observed in aqueous solution when using ^{1}H NMR spectroscopy.

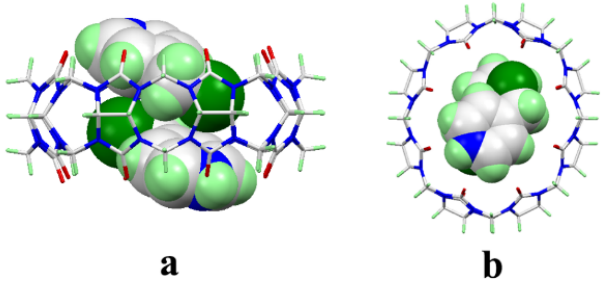

Figure 6. X-ray crystal structure of the inclusion complex **1** (a) side view; (b) top view.

In Figure 7a, it can be clearly evident that the encapsulated guest 4-chloromethylpyridine hydrochloride forms numerous hydrogen-bonds with the host Q[8]: the hydrogen-bonding interactions between the nitrogen or carbon atoms of the pyridyl with the portal carbonyl oxygen atoms of Q[8] exhibit distances for N(17)–H···O(6) at 2.271 Å, for C(27)–H···O(8) at 2.380 Å, for C(26)–H···O(1) at 2.583 Å, and for C(25)–H···O(2) at 2.613 Å. Moreover, a C(30)–H···O(4) distance of 2.478 Å is observed for the hydrogen-bonding interaction between the carbon atom of the chloromethyl and the portal carbonyl atom of Q[8]. As the Cl atom is an electron-withdrawing group, the density of the methylene cloud attached to the Cl atom decreases. This makes the methylene protons more positive and willing to form H-bonds with carbonyl oxygen of the Q[8]. In addition, there is an ion-dipole interaction between the positive nitrogen ion N(17) at the pyridine and the carbonyl oxygen atoms (O5 and O6) of the Q[8] host (Figure 7b), and the distance between N(17) and O(5) and O(6) is 3.069 Å and 2.870 Å, respectively. Interestingly, the guest molecule resides in a "sideways" fashion inside the Q[8] cavity, and the angle of the pyridine plane to the plane of the eight carbonyl oxygen atoms of the Q[8] portal is 22.38°. In other words, the abundant ion–dipole interactions and hydrogen-bonding interactions present here contribute to the formation of the stable inclusion complex **1**.

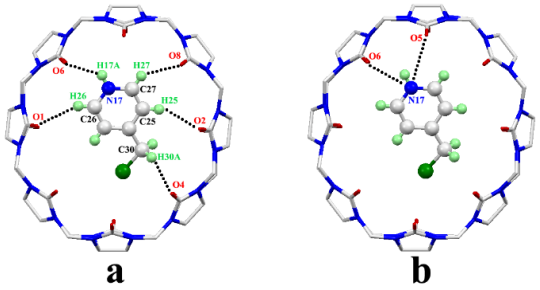

Figure 7. Ball-and-stick representation of compound showing guest molecules encapsulated into the Q[8] host, generating an inclusion complex. Solvate water molecules and chloride anions are omitted for clarity; only one guest molecule is shown here. C = light grey, O = red, N = blue, H = light green and Cl = green.

Conclusions

In summary, the results herein show that the host Q[8] can readily encapsulate the guest 4-chloromethylpyridine hydrochloride both in aqueous solution and in the solid state. The structure of the host-guest complex was verified by a multitude of methods including NMR spectroscopy, UV-visible spectroscopy, isothermal titration calorimetry (ITC), and single crystal X-ray crystallography. The results obtained indicated that the guest 4-chloromethylpyridine hydrochloride is encapsulated into the Q[8] cavity to a form 1:2 host-guest inclusion complex. This study not only enriches the recognition of chloromethylpyridine hydrochloride by macrocyclic host systems, but also provides a potential new method for the recognition of haloalkanes by macrocyclic compounds.

Experimental Section

Materials and apparatus

The guest 4-chloromethylpyridine hydrochloride was obtained from Sigma Aldrich and was used as supplied. Q[8] was prepared and purified according to a literature method.[36-37] All other reagents purchased were of analytical grade and were used as received. All the experiments performed herein employed double distilled water.

Isothermal titration calorimetry (ITC) measurements

A Nano ITC isothermal titration calorimeter (TA, USA) was employed to perform the microcalorimetric experiments in aqueous solution. The procedure for G with Q[8] involved 40 consecutive injections (6 μL) of the guest (2.0×10^{-3}mol/L) solution into the microcalorimetric reaction cell (1.3 mL) charged with the Q[8] solution (1.0×10^{-4} mol/L). The heat evolved was recorded at 298.15 K. The heat of reaction was corrected for the heat of dilution of the guest solution determined in separate experiments. Prior to the titration experiments, the solutions were degassed by sonication. Nano ITC analyze software was employed for the computer simulations (curve fitting).

UV-Vis absorption spectroscopy.

An Agilent 8453 spectrophotometer, operating at room temperature, was used to record the UV-vis absorption spectra of the host-guest complexes. The UV-vis absorption experiments were conducted using the following method: To a 10 mL volumetric flask were added 400μL of a 2.0×10^{-3}mol/L stock solution of G and various amounts of an aqueous 1.0×10^{-4}mol/L Q[8] solution, which was topped up to the final volume using distilled water. Samples of these solutions were combined to give solutions with an Q [8]/ G ratio of 0, 0.1, 0.2, 0.3. . . and 1.0. The Job's plot method was employed to determine the inclusion ratio present, $N_G:N_{(Q[8]+G)}$= 0, 0.1, 0.2, 0.3, . . ., 1.0.

^{1}H NMR spectroscopy.

The host-guest complexation of Q[8] and G was studied via the use of ^{1}H NMR spectra (including titration experiments), which were recorded in D_2O at 298.15 K using a JEOL JNM-ECZ400S 400 MHz NMR spectrometer (JEOL). Chemical shift values are reported in parts per million (ppm) relative to the internal standard TMS (0.0 ppm). ^{1}H NMR experiments were conducted using a Q[8] concentration of 5.0×10^{-4}mol/L.

Single-crystal X-ray crystallography.

A Bruker D8 VENTURE diffractometer employing graphite monochromatic Mo-*K*α radiation (λ = 0.71073 Å) was used to collect the data on **1**. Empirical absorption corrections were applied by using the multiscan program SADABS. Structural solution and full matrix least-squares refinement based on F^2 were performed with the SHELXS-*97* and SHELXL-*97* program packages, [38-40] respectively. Anisotropical thermal parameters were applied to all non-hydrogen atoms. Hydrogen atoms were treated as riding atoms with an isotropic displacement parameter equal to 1.2 times that of the parent atom. The SQUEEZE was employed given the disordered solvent water molecules present.[41] CCDC 2061709 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Crystal data for complex **1**. $[(C_{48}H_{48}N_{32}O_{16})@2(C_6H_7ClN)^+]\cdot16(H_2O)\cdot2Cl^-$, Mr = 1657.23, monoclinic, space group $P2_1/c$, a = 18.295(5) Å, b = 12.409(3) Å, c = 20.507(5) Å, β = 109.224(7)°, V = 4396.2(19) Å^3, Z = 2, Dc = 1.252 g cm^{-3}, F(000) = 1664, GOF = 1.359, R1 = 0.1178 (I > 2σ(I)), wR2 = 0.3894 (all data). CCDC 2061709. Anal. calcd for $C_{60}H_{62}C_{l4}N_{34}O_{16}$: C, 43.49; H, 3.78; N, 28.74. Found: C, 43.53; H, 3.74; N, 28.72.

Preparation of complex 1

Q[8] (15.8 mg, 0.011 mmol) was added to a solution of 4-chloromethylpyridine hydrochloride (10.5 mg, 0.064 mmol) in 3M HCl solution (3 mL). After stirring for 5 min at 60℃, the mixture was filtered. Following slow evaporation (*c.a*. 3 weeks) of the filtrate under air, rhombic colorless crystals of complex **1** were afforded. The data indicated that the guest 4-chloromethylpyridine hydrochloride is completely encapsulated in the cavity of the host Q[8], both in aqueous solution and in the solid state, generating a highly stable inclusion complex **1**.

Acknowledgements

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Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

There are no conflicts to declare.

Keywords: cucurbit[8]uril • 4-chloromethylpyridine hydrochloride • host–guest binding • inclusion complex • supramolecular self-assembly

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Layout 1:

FULL PAPER

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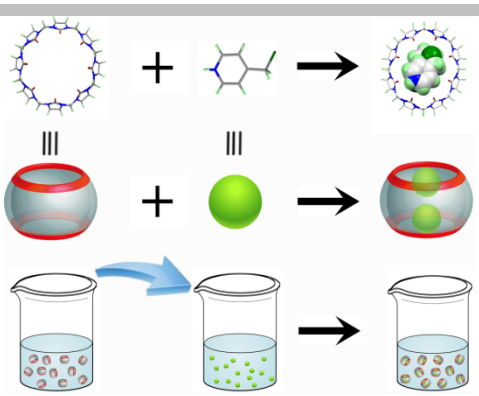

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