A study of the inclusion complex formed between cucurbit[8]uril and isonicotinic acid

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Abstract
The complexation between cucurbit[8]uril, Q[8], and isonicotinic acid has been studied using 1H NMR spectroscopy, UV–Vis absorption spectroscopy, Raman spectroscopy and single crystal X-ray diffraction. The results revealed that the 2:1 inclusion complex (4-PA)2@Q[8]·25H2O is formed, with two guests simultaneously encapsulated in the hydrophobic cavity; the mean planes of the guests are 3.535 Å apart.

Graphical abstract

Keywords Cucurbit[8]uril · Isonicotinic acid · Host–guest interaction · Ternary complex · X-ray structure

Introduction
Isonicotinic acid, also known as 4-pyridinecarboxylic acid (4-PA) is employed in the manufacture of both agrochemicals and pharmaceuticals, and is probably best known for its use in the production of Isoniazid, which is used to treat tuberculosis (TB) [1–5]. Whilst host–guest complexes of 3-pyridinecarboxylic acid (3-PA) with β-cyclodextrin are known [6], those for 4-pyridinecarboxylic acid tend to also involve thiocyanato coordination [7–10]. Isonicotinate ligands have also been employed as ligands/pillars in 3D arrays [11–13], in non-linear optical materials [14, 15], and in luminescent materials [16–18]. We are interested in the host–guest properties of cucurbit[8]urils [Q[8]]s [19, 20], and as part of this study, we have been investigated the inclusion ability of the Q[8] system. Given the size of the Q[8] cavity, there is the possibility of the encapsulation of more than one guest. A number of research groups have made use of this possibility, and have accessed intriguing ternary complexes. Examples include the work of Ko et al., [21] that featured the formation of supramolecular assemblies which utilized host-stabilized charge transfer interactions. The same type of interactions has also been exploited to
good effect in other work [22–27]. To-date, we have investigated the complexation of Q[8] with alkyl substituted 4-pyrrolidinopyridinium salts [28, 29], amino acids [30], and hemicyanine indole [31]. Moreover, in the case of the guests 1′,1″-(alkylene-1,4-diyl)bis(1-butyl)-4,4′-(bipyridine-1,1′-diium)bromide (alkylene = hexylene, octylene), supramolecular polymer formation was achieved via inclusion of alkyl chains [32, 33]. Moreover, we note that inclusion complexes of Isoniazid with tetramethylQ[6] and Q[7] have been reported, for which the guest either resides near the portal or is included in 1:1 fashion respectively [34, 35]. However, in the case of Q[8], poor aqueous solubility means that the presence of hydrochloric acid is often necessary, which in the case of isoniazid results in hydrolysis to isoniacin. Given this, herein, we have extended our studies to the interaction of Q[8] and isonicotinic acid (4-PA), see Fig. 1, and find that Q[8] can accommodate two 4-PA molecules thereby forming the inclusion complex (4-PA)$_2$@Q[8]·25H$_2$O.

Results and discussion

In order to investigate the complexation of Q[8] with 4-PA in solution, $^1$H NMR spectroscopic titration experiments were performed by adding increasing amounts of Q[8] to the solution of 4-PA in D$_2$O. As can be seen in the insert in Fig. 2, the protons Ha and Hb of the pyridyl ring experience an upfield shift, with that experienced by Hb been the greater (0.06 versus < 0.01 ppm). These observations are consistent with deep inclusion of the pyridyl ring, orientated such that the nitrogen end is nearer the cavity.

To more fully understand the interaction between Q[8] and 4-PA, UV titration experiments were conducted. Displayed in Fig. 3 are the UV spectra obtained for aqueous solutions containing a fixed concentration of 4-PA and variable concentrations of Q[8]. Furthermore, the Job’s plot is shown in Fig. 3c, and is consistent with a stoichiometry of 2:1.

The Raman spectra of the guest, Q[8] and their inclusion complex are presented in Fig. 4a; the detailed Raman assignments for pure Q[8] and complexes are summarized in Tables 1, 2. After complexing with 4-PA, two new peaks appeared near 1000 cm$^{-1}$, as shown in the Fig. 4b as green circles, which originate from 4-PA. The signature vibration frequency of C–N shifts slightly to higher wavenumbers in the complex as compared to pure Q[8] (Fig. 4c), and this is likely a reflection of the interaction between Q[8] and 4-PA.

Single crystal X-ray diffraction analysis reveals that the compound crystallizes in the tetragonal crystal system, space group $I4_1/a$. The asymmetric unit is shown in Fig. 5a, and the inclusion of guests by the complete macrocycle is shown in Fig. 5c; the crystal structure of the complex is composed of the host Q[8] molecule and two guests 4-pyridinecarboxylic acid. Crystallographic data is presented in Table 3. The mean planes of these molecules are 3.535 Å

![Fig. 1](structure.png) Structure of a the cucurbit[8]uril and b the guest 4-pyridine-carboxylic acid

![Fig. 2](nmr.png) $^1$H NMR spectra obtained from the titration of 4-PA with Q[8]: (I) Neat Q[8]; (II) Q[8]:4-PA = 1:2; (III) Pure 4-PA
apart. The Q[8] host has encapsulated two isonicotinic acid molecules in an off-set centrosymmetric embrace, bond lengths at the carboxyl group show this is the acid and not carboxylate. Other water was modelled using the Squeeze algorithm as a solvent mask in Olex2. The overall formula includes both ordered and disordered water molecules, and is (4-PA)₂@Q[8]·25H₂O. As can be seen in Fig. 5b, the encapsulated guest 4-pyridinecarboxylic acid forms multiple hydrogen-bonds with the host Q[8]: the hydrogen-bonding interactions between the carbon atoms of the pyridyl with the portal carbonyl oxygen atoms of Q[8] exhibit distances of C(29)–H⋯O(8) 2.443 Å, C(25)–H⋯O(6) 2.605 Å. The hydrogen of the carboxyl group in isonician forms hydrogen bonds with the oxygen atoms of the water molecule with an O(10)–H⋯O(1 W) distance of 1.563 Å. Meanwhile, there is also hydrogen-bonding between the oxygen atom of the water molecule and the portal carbonyl oxygen atoms of Q[8], the distance O(1 W)–H⋯O(5) is 2.092 Å.

As shown in Fig. 6, two adjacent complexes form a one-dimensional assembled host–guest supramolecular structure via hydrogen-bonding interactions between the portal carbonyl oxygen atom O5 of Q[8] and the coordinating water molecule O1W. Moreover, the carboxyl oxygen of isonician in one complex formed a hydrogen bond with a water molecule and those water molecules formed hydrogen bonds with the carbonyl oxygen of another complex. These hydrogen bonds further strengthen the stabilization of the crystal structure.

The layered two-dimensional structure is formed by one-dimensional supramolecular chains arranged in parallel to each other (Fig. 7). The hydrogen bonding interaction of the adjacent two layers of the supramolecular chains formed via the portal carbonyl oxygen atoms of Q[8] and the coordinating water molecule O1W. Moreover, the carboxyl oxygen of isonician in one complex formed a hydrogen bond with a water molecule and those water molecules formed hydrogen bonds with the carbonyl oxygen of another complex. These hydrogen bonds further strengthen the stabilization of the crystal structure.

In the crystal stacking diagram of the complex 4-PA@Q[8] along the a-axis direction (Fig. 8a), a supramolecular framework of numerous honeycomb-like channels consisting of one-dimensional supramolecular chain packing is observed; each channel in the framework is surrounded by six host–guest complexes. The framework structure is controlled by the presence of strong and directional hydrogen bonding, forming a two-dimensional network, which act as building blocks and further pack into a three-dimensional framework (Fig. 8b).
Conclusion

In summary, the results herein reveal that Q[8] can simultaneously hold two molecules of 4-pyridinecarboxylic acid in the hydrophobic cavity, both in solution (as shown by ¹H NMR and UV–vis spectra) and in the solid-state, as evidenced by a single crystal X-ray diffraction study. In the solid-state, extensive H-bonding results not only in the formation of 1D extended chains, but also 2D and 3D networks; water plays a central role in the formation of these networks.

Experimental section

Materials

General

The guest 4-pyridinecarboxylic acid (4-PA) was obtained from Aladdin (Shanghai, China). Q[8] was prepared and purified according to a literature method [36]. All other reagents were of analytical reagent grade and were used without any further purification. Deionized water was used throughout the experiments.

¹H NMR spectroscopy

All the ¹H NMR spectra, including those for the titration experiments, were recorded at 298.15 K on a JEOL JNM-ECZ400S 400 MHz NMR spectrometer (JEOL) in D₂O. D₂O was used as a field-frequency lock and the observed chemical shifts are reported in parts per million (ppm) relative to that for the internal standard (TMS at 0.0 ppm).

UV–Vis absorption spectroscopy

The UV–vis absorption spectra of the host–guest complexes were recorded using an Agilent 8453 spectrophotometer at room temperature. The aqueous solution of 4-PA was prepared with a concentration of 2.4 × 10⁻³ mol/L. An
aqueous solution of Q[8] was prepared with a concentration of 1.0 × 10^{-3} mol/L for absorption spectra determination. The UV–vis absorption experiments were performed as follows: 500 µL of a 2.4 × 10^{-3} mol/L stock solution of 4-PA and various amounts of an aqueous 1.0 × 10^{-3} mol/L Q[8] solution were transferred into a 10 mL volumetric flask, and then the volumetric flask was filled to the final volume with distilled water. Samples of these solutions were combined to give solutions with an N_{Q[8]}/N_{4-PA} = 0, 0.1, 0.2, 0.3, ..., and 1.0. The Job’s plot method was used to determine the inclusion ratio of the substance, N_{4-PA}/(N_{Q[8]} + N_{4-PA}) = 0, 0.1, 0.2, 0.3, ..., 1.0.

**Fig. 5**  
(a) Asymmetric unit with atoms drawn as 30% probability ellipsoids;  
(b) Ball-and-stick representation of compound showing guest molecules encapsulated into the Q[8] host, generating a inclusion complex. Most water molecules omitted, only one ordered molecule of water shown here. C = light gray, O = red, N = blue and H = light green;  
(c) Molecular structure of (4-PA)$_2$@Q[8]·25H$_2$O; most water molecules omitted for clarity;  
(d) Side view of the crystal structures

**Single-crystal X-ray crystallography**

Single-crystal data for compound were collected on the Bruker D8 VENTURE diffractometer with graphite monochromatic Mo-Kα radiation (λ = 0.71073 Å). 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-2014 program package, respectively [37, 38]. Anisotropical thermal parameters were applied to all the non-hydrogen atoms. All hydrogen atoms were treated as riding atoms with an isotropic displacement parameter equal to 1.2 times that of the parent atom. Final
structure refinement and modelling of the disordered water using a solvent mask were carried out with Olex2 [39].

Preparation of complex

Q[8] (7.54 mg, 0.005 mmol) was added to a solution of 4-pyridinecarboxylic acid (6.15 mg, 0.05 mmol) in HCl solution (5 mL, 6 mol/L). The mixture was heated until complete dissolution. Following slow evaporation of the volatiles from the solution over a period of about 3 weeks, block colorless crystals of complex were obtained.

SERS measurements

Raman spectra were carried out on WITec alpha300R confocal Raman microscopy (WITec GmbH). It operated at a laser (cobalt Laser) wavelength of 532 nm; 600-g/mm grating; scanning time of 30 s, with one accumulation; and laser power of 5 mW. Before the sample measurement, pure Q[8], 4-pyridinecarboxylic acid solid samples, and several better quality complex crystals were prepared, after placing the sample on a slide for compression, the sample can be measured.

Supplementary material

The crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2132077.
Fig. 6 One-dimensional supramolecular chain of the complex
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Declarations

Conflict of interest The authors declare no conflict of interest.

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Fig. 7 a Two-dimensional network of complex viewed down the c axis; b–e The interaction between two adjacent Q[8]

Fig. 8 a Two-dimensional network of complex viewed down the a axis; b Three-dimensional framework of complex
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