The Binding Behaviors between Cyclopentanocucurbit[6]uril and Three Amino Acids in the Solid and the Solution Phases

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Abstract

Binding behaviors between CyP₆Q[6] and three amino acids have been investigated by means of X-ray crystallography, proton nuclear magnetic resonance (¹H NMR) spectroscopy, amino acids and isothermal titration calorimetry (ITC). The results showed that CyP₆Q[6] forms a 1:2 inclusion complex with glycine, but 1:1 complexes with both leucine and lysine. Whereas the carboxyl group of glycine can enter the interior of the cavity of CyP₆Q[6], only the alkyl chains of leucine and lysine can enter this cavity. Interestingly, leucine can adopt two different self-assembly modes upon its interaction with cucurbituril, depending on the external conditions, whereas glycine and lysine do not exhibit such behavior.

Background And Originality Content

Cucurbit[*n*]urils (*n* = 5–8, 10, 14) are macrocyclic compounds with an inner hydrophobic cavity and two portals rimmed by polar carbonyl oxygen atoms, formed by multiple glycouril monomers doubly-bridged by methylene units.^[1-3] As fourth-generation supramolecular hosts following crown ethers, cyclodextrins, and calix[*n*]arenes, their high-affinity hydrophobic cavities have propelled their host-guest chemistry into the mainstream, making it a “hot spot” in cucurbituril chemistry. Because the hydrophobic cavities of cucurbiturils readily form stable inclusion complexes or rotaxane analogues, molecular capsules, and other supramolecular structures incorporating various organic small molecules,^[4-7] especially in aqueous systems, cucurbituril host-guest chemistry has played a significant role in the fields of drug delivery, chemical sensors, and cucurbituril supramolecular self-assembly materials.^[8-10] Most cucurbiturils show poor solubility in water, except, to some extent, cucurbit[7]uril, which has restricted their applications. The appearance of modified cucurbiturils, especially functionalized cucurbiturils with more water-soluble alkyl substituents and derivatives, has attracted ever more attention. With the emergence of modified cucurbiturils with excellent oil and water solubilities, the host-guest chemistry of cucurbiturils will gradually extend to other organic solvent systems, such as methanol, ethanol solution, and DMSO, and has played a vital role in functional application research.^[11-13] Cyclopentylcucurbit[6]uril (abbreviated as CyP₆Q[6], scheme 1) is a good oil- and water-soluble derivative, which has broad application prospects. However, as yet, there have been few studies on the synthesis and properties of cyclopentyl cucurbituril, and the research is still in its infancy.^[14-16]

Amino acids, the key constituents of protein/peptide bonds and important components of living systems, have always attracted much attention,^[17] and they have been widely studied in the host–guest chemistry of cucurbiturils. Because cucurbit[*n*]urils have both electronegative carbonyl oxygen-fringed portals and a hydrophobic cavity,^[18,19] their ion-dipole and hydrophobic effects make them well-suited to form host–guest complexes with amino acids. Mutihac and Dearden found that cucurbit[6]uril readily binds to some amino acids with hydrophobic side chains.^[20,21] Kovalenko and Kim studied the binding behavior between cucurbit[7]uril and amino acids with different side chains in the gas and liquid phases, respectively, and observed different binding affinities under different conditions.^[22,23] Both Bush and Nau found that the larger cavity of cucurbit[8]uril can selectively bind a small organic molecule and an amino

acid simultaneously.^[24,25] Our research group reported the host-guest binding behavior of twisted cucurbit[14]uril and inverted cucurbit[7]uril with amino acids,^[26,27] and for the first time reported supramolecular complexes of cucurbituril and enantiomeric amino acids.^[28]

In recent years, studies on the binding behavior between macrocyclic compounds, such as cyclodextrin and crown ethers, and amino acid molecules have been extremely widespread.^[29-31] However, the research on the host-guest chemistry of cyclopentyl cucurbiturils is still immature, so we are interested in the study on the host-guest properties of CyP₆Q[6] and amino acids. For the present study, we took CyP₆Q[6] as the host, and selected three different amino acids, namely glycine (Gly), L-lysine (L-Lys), and L-leucine (L-Leu), as guests. We examined the binding behavior between these components in the solid and liquid phases (Scheme 1).

Results And Discussion

2.1 Binding modes between CyP₆Q[6] and amino acids in the solution phase

Fig. 1 shows the crystal structure of Gly@CyP₆Q[6] (complex **1**). Analysis of the single-crystal structure shows that complex **1** belongs to the triclinic system with the centrosymmetric space group *P*-1. An oak ridge thermal-ellipsoid plot program (ORTEP) representation of the asymmetric unit is shown in the Supporting Information (Fig. S1). It contains two halves of CyP₆Q[6], two protonated glycine molecules, and one free [CdCl₄]²⁻ ion. In the single-crystal structure of complex **1**, each CyP₆Q[6] contains two glycine molecules. The carboxyl group of each glycine molecule is included in the cavity of the CyP₆Q[6], but its amino and methylene groups remain outside. The nitrogen atoms (N26 and N13) of the respective glycine molecules form two hydrogen bonds with two portal oxygen atoms (O5, O6 and O15, O16) of CyP₆Q[6], and the N–H···O distances are in the range 2.752–3.035 Å. It is interesting to note that a hydrogen bond is established between the nitrogen atom of a glycine molecule included by the cucurbituril and a chlorine atom (Cl1) of the counter ion [CdCl₄]²⁻, with an N–H···Cl distance of 3.228 Å. This is not the case for the other amino acid molecule included by the cucurbituril. At the same time, there is also a dipolar interaction between this counter ion and a methylene proton on the outer wall of the other cucurbituril molecule. [CdCl₄]²⁻ thus acts as a bridging unit to link the cucurbituril with the amino acid (shown by purple dotted lines in Fig. 1).

Fig. 2 shows the crystal structure of L-Lys@CyP₆Q[6] (complex **2**). Analysis of the single-crystal structure shows that complex **2** belongs to the monoclinic system with centrosymmetric space group *P*2₁/*c*. An ORTEP representation of the asymmetric unit is shown in Fig. S2. It contains half of CyP₆Q[6], a protonated lysine molecule (occupancy ratio 0.5), and a free [CdCl₄]²⁻ ion. In the single-crystal structure of complex **2**, each CyP₆Q[6] contains a lysine molecule. The carboxyl and amino groups of this lysine molecule, and the carbon atom (C2) to which they are bound, lie outside of the portal of CyP₆Q[6], while the rest of the molecule is within the cavity. The amino nitrogen atom (N1) and hydroxyl oxygen atom

(O2) of the lysine molecule outside of the portal of CyP₆Q[6] form four hydrogen bonds (N1-H1C...O4, N1-H1A...O6, N1-H1C...O7, and O2-H2...O7) with three oxygen atoms (O4, O6, and O7) of a portal of CyP₆Q[6], with lengths in the range 2.334–3.062 Å. The nitrogen atom (N2) of the terminal amino group of lysine inside the cavity forms a hydrogen bond with a portal carbonyl oxygen atom of the cucurbituril with a distance of 2.952 Å. Unlike in complex **1**, the counter ion does not interact with the amino acid in this complex, but only surrounds the cucurbituril through dipole interactions (Fig. S5).

Fig. 3 shows the crystal structure of L-Leu@CyP₆Q[6] (complex **3**). Complexes **3** and **4** both comprise leucine and CyP₆Q[6]. Complex **3** belongs to the triclinic system with chiral space group *P*1, whereas complex **4** belongs to the monoclinic system with chiral space group *C*2. The main part of the asymmetric unit of these two complexes is composed of a CyP₆Q[6] host and a leucine molecule, and has the same binding mode. The difference is that the counter ion of complex **3** (Fig. S3) is [ZnCl₃·H₂O][−], whereas that of complex **4** (Fig. S4) is [ZnCl₄]^{2−}. Structural analysis of the main parts of these two complexes (taking complex **3** as an example; Fig. 3) shows that there is a hydrogen bond between the hydroxyl oxygen (O13) of the leucine molecule and a portal carbonyl oxygen (O1) of the cucurbituril, with an O13–H13...O1 distance of 2.629 Å. There are also hydrogen bonds between the amino nitrogen (N25) of the leucine molecule and three portal carbonyl oxygen atoms (O5, O7, O9) of the cucurbituril, with distances in the range 2.740–2.890 Å.

The counter ions of complex **3** are paired around the cucurbituril by ion-dipole interactions, and there is also an ion-dipole interaction between the two paired counter ions. Although the counter ions of complex **4** also surround the cucurbituril through ion-dipole interactions, there is no weak interaction between them. This difference results in very different stacking patterns of these two complexes. Fig. 4 shows stack views of complexes **3** and **4** along the *c*-axis. From Fig. 4a, b, it can clearly be seen that all of the cucurbituril units in complex **3** have the same orientation, whereas those in complex **4** have two orientations with an included angle of 67.9°. Due to the different orientations of the cucurbituril moieties, there is a significantly larger channel along the *c*-axis in complex **4** than in complex **3**.

2.2 Interactions between CyP₆Q[6] and amino acids in the solution phase

CyP₆Q[6] shows good solubility in many solvents, most notably in water, in which it is 1 to 2 orders of magnitude more soluble than ordinary cucurbituril. Because the amino acids that make up the protein required for animal nutrition are mostly present in aqueous systems, the good water solubility of CyP₆Q[6] facilitates the study of its interactions with amino acids. In the present work, the binding behavior of CyP₆Q[6] with the above three amino acids was investigated in D₂O. In ¹H NMR, the cavity of CyP₆Q[6] has a shielding effect on proton signals, whereas outside of the portals, in the vicinity of the carbonyl oxygen atoms, the proton signals are subjected to a deshielding effect. According to this theory, analysis of the ¹H chemical shifts and splittings of the signals of protons of amino acids and the host provides insight into the binding mode between them. Fig. 5 shows the changes in the ¹H NMR spectrum of the guest Gly as it is dropped into a solution of the host CyP₆Q[6]. The results show that the peak due to the α

protons of Gly shifts upfield, indicating that this unit enters the cavity of the cucurbituril. Considering the ion-dipole and hydrophobic effects, it may be speculated that the carboxyl group and methylene unit of Gly enter the cavity, while the amino group is fixed at the portal of CyP₆Q[6]. This binding mode is basically similar to the crystal structure in the solid phase. However, a difference is that the methylene unit lies outside of the portal in the solid phase, but inside the cavity in the liquid phase. At up to two molar equivalents of Gly with respect to CyP₆Q[6], the α protons show only one signal. Beyond two molar equivalents, two signals due to this unit appear, corresponding to bound and free Gly. This indicates that CyP₆Q[6] and Gly form a 1:2 inclusion complex, and that the exchange frequency is slower than the operating frequency of the ¹H NMR spectrometer.

The changes in the ¹H NMR spectrum of the guest L-Leu upon its incremental addition to CyP₆Q[6] are shown in Fig. 6. Two sets of proton resonances for L-Leu are observed, indicating that the frequency of binding and release of L-Leu in CyP₆Q[6] is slower than the operating frequency of the ¹H NMR spectrometer, consistent with the observations for Gly. A difference is that the α proton signals of L-Leu shift downfield, whereas the signals of the remaining alkyl chain protons shift upfield, suggesting that only the alkyl chain of L-Leu enters cucurbituril, while the carboxyl group remains outside of the portal. At the same time, it can be further seen in Fig. 6 that the ϵ and λ proton signals of the two methyl groups are split into two groups of signals from the original overlapping signal, indicating that these methyl groups are in different positions in the cucurbituril. A similar splitting is seen for the β and γ proton signals. After L-Leu interacts with the cucurbituril, the environment of the two hydrogen protons of β protons will have a certain difference, causing it to split into two sets of signals, so three peaks due to the β and γ protons are seen. When a sub-stoichiometric amount of L-Leu is added to CyP₆Q[6], it displays only one set of signals. Once it is in excess, another set of signals due to free L-Leu appears. This indicates that CyP₆Q[6] forms a 1:1 complex with L-Leu, as in the solid-phase crystal structure.

As shown in Fig. 7, titration ¹H NMR spectroscopy was also used to investigate the binding behavior between CyP₆Q[6] and L-Lys. Similarly to L-Leu, the α proton signals of L-Lys shift downfield, while the signals of the other alkyl chain protons shift upfield, indicating that its alkyl chain enters the cavity of the cucurbituril, while the two amino groups are fixed at the portals, forming a structure similar to that of butanediamine@CyP₆Q[6]. The methine unit at which the carboxyl α proton is linked to one of the amino groups remains outside of the portal, forming a 1:1 complex of L-Lys@CyP₆Q[6]. The cavity of CyP₆Q[6] is large enough to accommodate the L-Lys alkyl chain in its fully extended form, as corroborated by the crystal structure. It is worth noting that during the titration process, when the amount of L-Lys added reached 0.5 equivalents with respect to CyP₆Q[6], its peaks suddenly broadened and even disappeared. This phenomenon may feasibly be attributed to the exchange frequency of L-Lys in and out of the cavity of the cucurbituril exceeding the operating frequency of the ¹H NMR spectrometer, such that the detected ¹H NMR signals are averages of various intermediate states of the host–guest interaction. Averaging over a multitude of states will make the signals of the guest tend towards the baseline. Of course, it may also

be enrichment of lysine that causes the disappearance of the signal of the guest proton. The specific cause is still unclear, and further research is needed.

2.3 Isothermal titration calorimetry

Isothermal titration calorimetry (ITC) experiments (Fig. S8) were performed to determine the thermodynamic parameters of the above three amino acids and CyP₆Q[6] in water, providing insight into the thermal stability and driving force of the interactions. Table 1 shows that the enthalpies and entropies of the interactions of the three amino acids with CyP₆Q[6] are both negative. From the contributions of these two thermodynamic parameters to the Gibbs free energy, it can be seen that the three systems are enthalpy-driven, and the driving force is determined by the ion-dipole interaction and the hydrophobic effect. The alkyl chain of the amino acid is more inclined to enter the cavity of the host due to the hydrophobic effect, allowing water molecules originally in the cavity of the CyP₆Q[6] to enter the aqueous phase, thereby reducing the entropy of the system. Moreover, 2Gly@CyP₆Q[6] evidently has the largest binding constant among the three studied systems, which may be due to the fact that there is some interaction between the two amino acids in addition to the interaction between glycine and cucurbituril. Its crystal structure (Fig. 1) shows that the carboxyl groups of both glycine molecules are also involved in hydrogen bonds, forming a more stable structure, so their binding constants are an order of magnitude higher than those for the other two amino acids. For lysine and leucine with the same number of carbon atoms, the binding constants are relatively close, but that of lysine is slightly higher due to a dipolar interaction of the amino groups.

Conclusion

In summary, we have investigated the binding behavior between CyP₆Q[6] and three amino acids in both the solid and liquid phases. For lysine and leucine, both X-ray crystallography and ¹H NMR spectroscopy indicate the formation of 1:1 host-guest complexes, with the respective alkyl chains within the cavity of CyP₆Q[6]. Glycine is bound slightly differently in the two phases; although a 1:2 inclusion complex is formed in each case, the methylene units have different locations. In the crystal structure, the methylene units lie outside of the portals, whereas solution ¹H NMR shows that they lie within the cavity of the cucurbituril. ITC shows that binding of all three amino acids is enthalpy-driven. Leucine shows two self-assembly modes, but this is not seen for the other two amino acids. The results of these experiments not only add to the understanding of the molecular recognition of amino acids, but are also of value for the design and synthesis of new bioactive cucurbiturils for the purpose of biological recognition and simulation.

Experimental

4.1 Materials and methods

All raw materials used in this study were purchased from Aladdin Industrial Corporation (AR, Shanghai, China). CyP₆Q[6] was prepared according to a literature procedure.^[14]

4.2 Preparation of complexes 1–4

Complex 1: Preparation of CyP₆Q[6]@2Gly@[CdCl₄]²⁻ crystals. CyP₆Q[6] (10 mg, 8.1 μmol), Gly (5.76 mg, 72.9 μmol), and CdCl₂·2H₂O (7.2 mg, 32.4 μmol) were added to 3 M HCl (3 mL), and the solution was boiled for about 1 min. It was then filtered, and the filtrate was left to stand at room temperature. After several days, single crystals of CyP₆Q[6]@2Gly@[CdCl₄]²⁻ suitable for X-ray diffraction analysis were obtained in 38% yield.

Complex 2: Preparation of CyP₆Q[6]@L-Lys@[CdCl₄]²⁻ crystals. CyP₆Q[6] (10 mg, 8.1 μmol), L-Lys (10.8 mg, 72.9 μmol), and CdCl₂·2H₂O (7.2 mg, 32.4 μmol) were added to 3 M HCl (3 mL) and the solution was boiled for about 1 min. It was then filtered, and the filtrate was left to stand at room temperature. After several days, single crystals of CyP₆Q[6]@L-Lys@[CdCl₄]²⁻ suitable for X-ray diffraction analysis were obtained in 42% yield.

Complex 3: Preparation of CyP₆Q[6]@L-Leu@[ZnCl₃·H₂O]⁻ crystals. CyP₆Q[6] (10 mg, 8.1 μmol), L-Leu (9.6 mg, 72.9 μmol), and ZnCl₂·2H₂O (5.6 mg, 32.4 μmol) were added to 2.5 M HCl (3 mL), and the solution was heated for about 1 min. It was then filtered, and the filtrate was left to stand at room temperature. After several days, single crystals of CyP₆Q[6]@L-Leu@[ZnCl₃·H₂O]⁻ suitable for X-ray diffraction analysis were obtained in 32% yield.

Complex 4: Preparation of CyP₆Q[6]@L-Leu@[ZnCl₄]²⁻ crystals. CyP₆Q[6] (10 mg, 8.1 μmol), L-Leu (9.6 mg, 72.9 μmol), and ZnCl₂·2H₂O (5.6 mg, 32.4 μmol) were added to 3 M HCl (3 mL), and the solution was boiled for about 1 min. It was then filtered, and the filtrate was left to stand at room temperature. After several days, single crystals of CyP₆Q[6]@L-Leu@[ZnCl₄]²⁻ suitable for X-ray diffraction analysis were obtained in 35% yield.

All of the obtained crystals were examined on a Bruker single-crystal diffractometer, and the crystallographic parameters are shown in Table S1. The CCDC numbers of complexes **1–4** are 1977303–1977306, respectively.

4.3 ¹H NMR spectroscopy

Gly, L-Leu, L-Lys, and CyP₆Q[6] were each dissolved in D₂O. The amount of CyP₆Q[6] was kept fixed at 1 mM in all studies. The amino acid solution was added dropwise to the CyP₆Q[6] solution to excess, and ¹H NMR spectra were recorded at appropriate intervals on a JEOL JNM-ECZ400s spectrometer at 25 °C. D₂O was used as a field-frequency lock, and the observed chemical shifts are reported in parts per million (ppm) relative to D₂O as an internal standard (δ=4.67 ppm).

4.4 Isothermal titration calorimetry

A 1.00×10^{-4} mol/L solution of CyP₆Q[6] in water (1.00 mL) was placed in the sample cell, and a 1.00×10^{-3} mol/L Gly solution was drawn into a 250 mL syringe. The temperature was set at 25 °C, and the titration was conducted by adding 30 aliquots (6 µL) of the Gly solution at intervals of 300 s.

A 1.00×10^{-3} mol/L solution of CyP₆Q[6] in water (1.00 mL) was placed in the sample cell, and a 1.00×10^{-2} mol/L L-Leu (L-Lys) solution was drawn into a 250 mL syringe. The temperature was set at 25 °C, and the titration was conducted by adding 25 aliquots (10 µL) of the L-Leu (L-Lys) solution at intervals of 300 s. The thermodynamic parameters of each system were determined on a Nano ITC isothermal calorimeter. After deleting the first two unwanted data points, the data were analyzed with ORIGIN 8.0 software using an independent model.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials.

All data and materials are all provided.

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Competing interests

The authors declare no conflicts of interest.

Contributions

SYC performed all lab work related to obtaining of compound and chemical assay, and wrote the highest percentage of the manuscript. WWZ analyzed and refined all crystal structures and wrote related content. XNY revised the manuscript. LTW conducted the synthesis of the main substance. ZT guided the technical methods involved in the manuscript. PHM was the leader of the project, holds the original idea,

designed the statistical experiments and coordinated the experimental activities among all engaged labs. All authors read and approved the final manuscript.

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Abbreviations

CyP₆Q[6]: cyclopentanocucurbit[6]uril

ITC: isothermal titration calorimetry

¹H NMR: proton nuclear magnetic resonance

Gly: glycine

L-Lys: L-lysine

L-Leu: L-leucine

ppm: parts per million

TMS: tetramethylsilane

ORTEP: oak ridge thermal-ellipsoid plot program

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Tables

Table 1. Thermodynamic parameters of the interactions of amino acids with CyP₆Q[6]

Experiment	ΔH (KJ/mol)	$T\Delta S$ (KJ/mol)	K_a (m ⁻¹)
Gly-CyP ₆ Q[6]	-48.47	-15.42	6.15×10^5
l-Leu-CyP ₆ Q[6]	-59.11	-34.82	1.80×10^4
l-Lys-CyP ₆ Q[6]	-35.66	-10.85	2.23×10^4

Figures

Figure 1

Host-guest interaction of complex 1.

Figure 2

Host-guest interaction of complex 2.

Figure 3

Binding mode of leucine and cucurbituril in complexes 3 and 4.

Figure 4

a) Stack view of complex 3 along the c-axis; b) stack view of complex 4 along the c-axis.

Figure 5

Titration ^1H NMR spectra of Gly, in the presence of CyP6Q[6] (1 mM), with (a) 0.00, (b) 1.24, (c) 2.31 equiv. of Gly, (d) neat Gly.

Figure 6

Titration ^1H NMR spectra of L-Leu, in the presence of CyP6Q[6] (1 mM), with (a) 0.00, (b) 0.35, (c) 0.89, (d) 1.21 equiv. of L-Leu, (e) neat L-Leu.

Figure 7

Titration ^1H NMR spectra of L-Lys, in the presence of CyP6Q[6] (1 mM), with (a) 0.00, (b) 0.20, (c) 0.50, (d) 0.70 equiv. of L-Lys, (e) neat L-Lys.

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