ARTICLE

Encapsulation of L-Valine, D-Leucine and D-Methionine by Cucurbit[8]uril

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Zeng-Hui Zhang,[a] Rui-Lian Lin,[b] Xiang-Yun Yu,[a] Li-Xia Chen,[a] Zhu Tao,[a] Xin Xiao,*[a] Gang Wei,*[c] Carl Redshaw,[d] and Jing-Xin Liu *[b]

The binding interactions of cucurbit[8]uril (Q[8]) with L-Valine, D-Leucine, and D-Methionine, both in aqueous solution and solid state, have been studied by ^{1}H NMR spectroscopy and X-ray crystallography. ^{1}H NMR data indicate that Q[8] can encapsulate these three kinds of amino acids in aqueous solution. X-ray crystallography reveals how the Q[8] binds with the amino acids to form inclusion complexes L-Val$_2$@Q[8], D-Leu$_2$@Q[8], and D-Met$_2$@Q[8] through host-guest interactions. It was also found that the deformation degree of the Q[8] host is related to the molecular size of the encapsulated guests.

Introduction

As the basic building blocks of peptides and proteins, the twenty natural amino acids play fundamental and significant roles in sustaining life on earth. The deletion of any amino acid may lead to some diseases. Therefore, the recognition and inclusion of amino acids by artificial containers has attracted a lot of attention from scientists.[1-5] Until now, a number of macrocyclic hosts including cyclodextrins, cyclophanes, calix[*n*]arenes and pillar[*n*]arenes have been explored in order to recognize and encapsulate amino acids.[6-8] Our efforts in the area of amino acid recognition involve the use of cucurbit[*n*]urils (*n* = 5–8, 10, abbreviated as Q[*n*], Figure 1), a family of macrocyclic molecules comprised of *n* glycoluril units bridged by 2*n* methylene groups.[9-14] Each Q[*n*] molecule possesses two identical portals and a rigid hydrophobic cavity, which can selectively accommodate and bind guest molecules. Over the past decade, we and others have studied the capacity of Q[*n*]s and their derivatives to recognize specific amino acids, peptides and proteins.[15-27]

It is well-known that the larger Q[*n*] homologue Q[8] has a spacious hydrophobic cavity, which can accommodate two aromatic groups simultaneously.[28] In theory, the Q[8] cavity also has the capability of encapsulating a pair of amino acids. With this idea in mind, we have started to address two important issues. Firstly, how does the shape and size of the amino acid affect the binding of the Q[8] to the amino acid? Secondly, does the chirality of the amino acid affect the binding of the Q[8] to the amino acid? Here, three specific amino acids, L-Valine (L-Val), D-Leucine (D-Leu), and D-Methionine (D-Met) were chosen as the guests. In the present work, the binding interactions of the Q[8] host with these three amino acids in aqueous solution is investigated by ^{1}H NMR spectroscopy. In particular, single crystals of these three amino acids complexed with the Q[8] host have been prepared. The X-ray crystallography clearly shows how the Q[8] host can encapsulate the amino acids to form homoternary inclusion complexes through host-guest interactions. Significant ellipsoidal deformation of the Q[8] host was also observed in these inclusion complexes. Structural comparison of the homoternary inclusion complexes reveals that the deformation degree of the Q[8] host depends on the molecular size of the encapsulated amino acids. The purpose of this article is to probe the recognition properties of the Q[8] host toward amino acids.

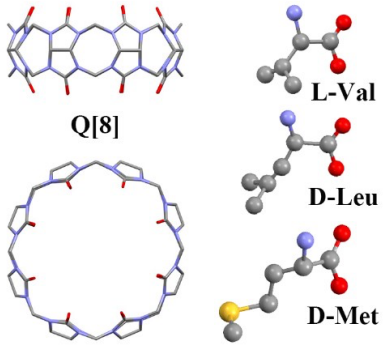

Figure 1. The structures of Q[8] and the amino acids used in this study.

[a] *Key Laboratory of Macrocyclic and Supramolecular Chemistry of Guizhou Province, Guizhou University, Guiyang 550025, P. R. China. E-mail: gyhxxiaoxin@163.com*
[b] *College of Chemistry and Chemical Engineering, Anhui University of Technology, Maanshan 243002, P. R. China. E-mail: jxliu411@163.com*
[c] *CSIRO Mineral Resources, PO Box 218, Lindfield, NSW 2070, Australia. E-mail: gang.wei@csiro.au*
[d] *Department of Chemistry, University of Hull, Hull HU6 7RX, U.K*

† CCDC 2122314, 2122315 and 2122316 for compounds **1**-**3**. For crystallographic data in CIF or other electronic format see DOI: 10.1039/XXXXX.

Results and Discussion

Binding interactions of Q[8] with L-Valine, D-Leucine, and D-Methionine in aqueous solution

The binding interactions of the Q[8] host with the guests L-Valine, D-Leucine, and D-Methionine in aqueous solution were monitored by ^{1}H NMR spectroscopic methods. Given the Q[*n*] cavity is a proton-shielding region, when the guest is encapsulated into the Q[*n*] cavity, the proton signals of the guest will shift upfield. By contrast, the outside of the portals of Q[*n*] are a proton-deshielding region. Accordingly, it is convenient to deduce the binding models of the Q[8] host with the amino acid guests from changes in their ^{1}H NMR spectra. As shown in Figure 2, upon the addition of increasing amounts of Q[8] host, all the proton signals of the L-Valine gradually shift upfield, indicating that the L-Valine is encapsulated into the Q[8] cavity.

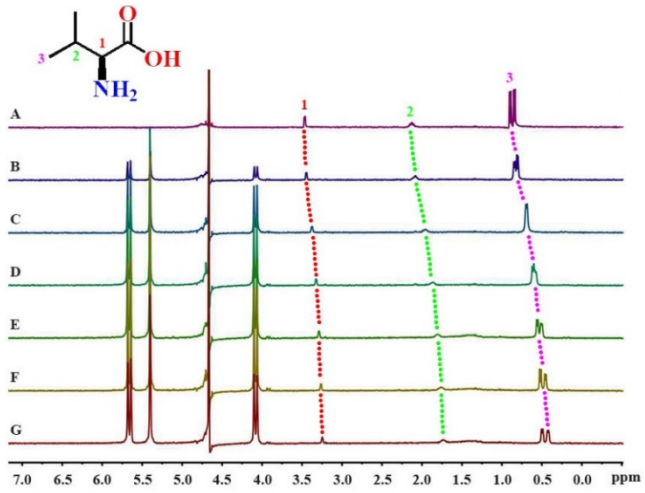

Figure 2. ^{1}H NMR spectra (400 MHz, D_2O) of L-Valine (A, 0.5 mmol·L^{-1}) in the absence and in the presence of (B) 0.15, (C) 0.52, (D) 0.97, (E) 1.55, (F) 1.92 and (G) 2.12 equiv. of Q[8] in D_2O at 20 °C.

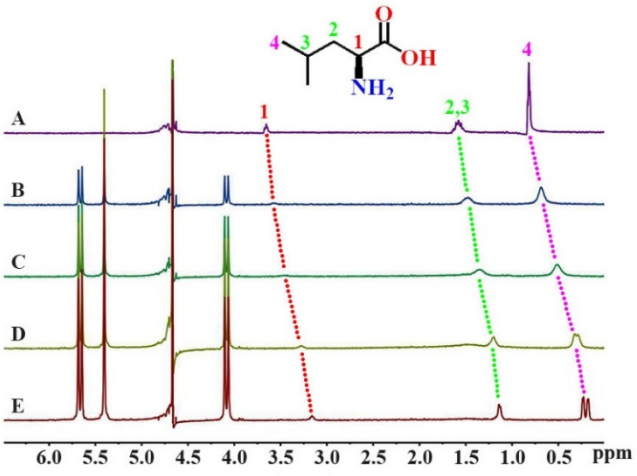

Figure 3. ^{1}H NMR spectra (400 MHz, D_2O) of D-Leucine (A, 0.5 mmol·L^{-1}) in the absence and in the presence of (B) 0.28, (C) 0.76, (D) 1.54 and (E) 2.15 equiv. of Q[8] in D_2O at 20 °C.

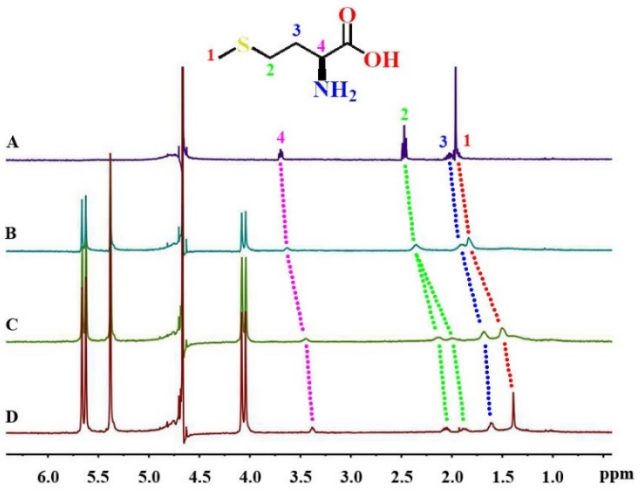

Figure 4. ^{1}H NMR spectra (400 MHz, D_2O) of D-Methionine (A, 0.5 mmol·L^{-1}) in the absence and in the presence of (B) 0.57, (C)1.41 and (D) 2.02 equiv. of Q[8] in D_2O at 20 °C.

The binding behaviour of Q[8] with D-Leucine and D-Methionine is illustrated in Figures 3 and 4, and these are similar to our observations for Q[8] with L-Valine. In the other words, both D-Leucine and D-Methionine can also be encapsulated into the Q[8] cavity in aqueous solution. There is no doubt that the major driving forces for the formation of the Q[8]-based inclusion complexes will be hydrophobic effects. Meanwhile, the van der Waals interaction between the surfaces of the amino acids and the inner wall of the Q[8], the ion-dipole interactions between the ammonium group of the amino acids and the carbonyl groups on the Q[8] portal as well as hydrogen bonds between the amino acids, may all also contribute to the formation of the Q[8]-based inclusion complexes.

To better understand the host-guest interactions between Q[8] and these 3 amino acids, we carried out isothermal titration calorimetry (ITC) experiments at 298.15 K. Table S1 and Figure S1–S3 show the equilibrium association constants (K_a) and thermodynamic parameters for the Q[8]-amino acid systems for L-Valine, D-Leucine, and D-Methionine. The experimental results revealed the association constant (K_a) for the complexes of the amino acids with the Q[8] to be 5.847×10^7, 7.648×10^7 and 2.825×10^7 M^{-2}, respectively, which indicates strong binding between the Q[8] and the three amino acids.

Structural Analysis of Inclusion Complexes in the Solid State.

We also examined the binding behaviour of the Q[8] host and with the L-Valine, D-Leucine, and D-Methionine guests in the solid state by X-ray crystallography (see experimental section). Slow vapour evaporation of aqueous HCl solutions containing the Q[8] host and the corresponding amino acid guest in the presence of $CdCl_2$ (see experimental section) successfully afforded single crystals of the inclusion complexes $(C_5H_{12}NO_2)^+_2$@Q[8]·2$[CdCl_4]^{2-}$·2$(H_3O)^+$·12H_2O (**1**), $(C_6H_{14}NO_2)^+_2$@Q[8]·2$[CdCl_4]^{2-}$·2$(H_3O)^+$·12H_2O (**2**), and $(C_5H_{12}NO_2S)^+_2$@Q[8]·Q[8]·2$[CdCl_4]^{2-}$·2$(H_3O)^+$·18H_2O (**3**).

Single crystal X-ray diffraction analysis reveals that compound **1** crystallizes in the monoclinic crystal system, space group $P2_1/c$. The asymmetric unit of the compound **1** contains one half of the Q[8] host, one protonated Val molecule, one tetrahedral $[CdCl_4]^{2-}$ anion, and seven lattice water molecules. As shown in Figure 5, two protonated L-Val molecules were encapsulated into the Q[8] host, forming a homoternary inclusion complex L-Val_2@Q[8], in agreement with what we observed in aqueous solution. The ammonium group of the L-Val molecule points toward two carbonyl oxygen atoms of the Q[8] host. One proton of the ammonium group is involved in hydrogen bonding with one carbonyl oxygen atom, with an N–H···O distance of 2.219 Å. The other two protons of the ammonium group form hydrogen bonds with solvent water molecules. At the same time, the carboxyl group on the other side of the L-Val molecule forms a hydrogen bond with a water molecule (O2W), which links with two carbonyl oxygen atoms (O3 and O8) at the portal of the Q[8] host through hydrogen bonds. Given that the encapsulated L-Val molecule is protonated, there must be electrostatic interactions and van der Waals contacts between the guest molecules and the Q[8] host, as we previously reported.[29]

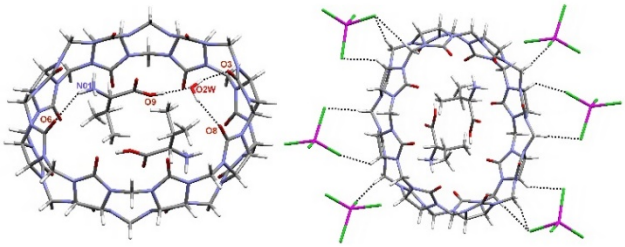

Figure 5. Crystal structure of the inclusion complex L-Val_2@Q[8] (left) and its surroundings (right).

Analysis of the extended structure of the compound **1** reveals that each inclusion complex L-Val_2@Q[8] is surrounded by eight repeating units and six tetrahedral $[CdCl_4]^{2-}$ counterions (Figure 5). Each $[CdCl_4]^{2-}$ anion form strong C–H···Cl contacts with three Q[8] hosts. The neighbouring Q[8] hosts interact with each other via C–H···O hydrogen bonding of the methine or methylene groups at the outer surface of the Q[8] host with carbonyl oxygens from neighbouring Q[8] hosts. Both the C–H···Cl contacts and the C–H···O hydrogen bonds contribute to stabilizing the structure of compound **1**, and these are classified as "outer-surface interactions".[30]

The crystal structure of compound **2** is very similar to that of compound **1**. It crystallizes in the space group of $P2_1/c$, and contains a homoternary inclusion complex D-Leu_2@Q[8] in the asymmetric unit. However, closer inspection reveals an important difference between these two inclusion complexes. The nitrogen atom of the D-Leucine in D-Leu_2@Q[8] is out of the mean plane of the Q[8] portal by about 1.147 Å, which is a much larger value than that of the L-Valine in L-Val_2@Q[8] (0.952 Å, Figure 6). Obviously, part of the D-Leucine molecule is squeezed out of the Q[8] cavity because the D-Leucine molecule is larger than the L-Valine molecule.

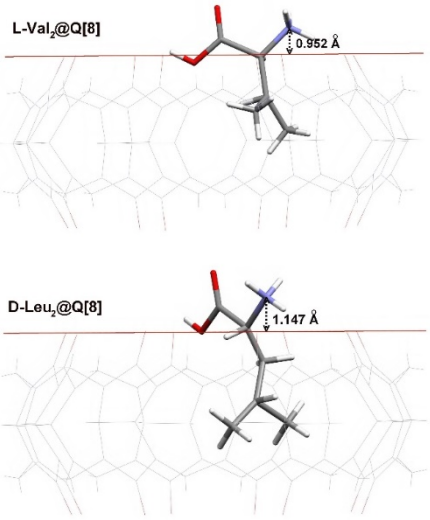

Figure 6. The distance of the nitrogen atom out of the mean plane of the Q[8] portal.

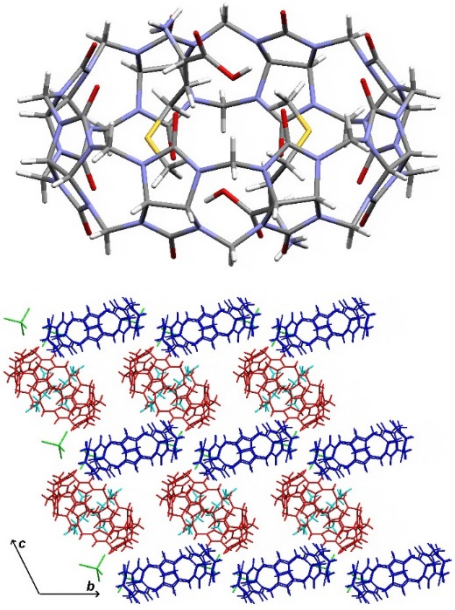

Figure 7. Crystal structure of the inclusion complex D-Met_2@Q[8] (up) and 2D planar structure of compound **3** viewed down the *a* axis (down).

The X-ray crystallography confirms that compound **3** crystallizes in the triclinic space group *P*-1. There are two crystallographically independent Q[8] hosts in the asymmetric unit of compound **3**. One of them accommodates two D-Methionine molecules and generates a homoternary inclusion complex D-Met_2@Q[8], the other accommodates some disorder water molecules or is empty. As can be seen in Figure 7, the two D-Methionine guests are located inside the Q[8] cavity. Both the ammonium group and the carboxyl group point toward the Q[8] portal. They form hydrogen bonds with the carbonyl oxygens of the Q[8] host or the solvent water molecules (N···O and O···O distances in the ranges of 2.833(5)-

3.097(6) Å). It is worth mentioning that in compound **3**, each Q[8] host of the inclusion complex D-Met$_2$@Q[8] forms numerous C–H···O hydrogen bonds with four neighbouring empty Q[8] hosts. At the same time, the empty Q[8] hosts also connect with four inclusion complexes through C–H···O hydrogen bonds. As a result, they form an interesting grid-like planar structure, parallel to the *bc*-plane of the unit cell, as shown in Figure 7. The stacking of the planar structure further generates numerous 1-D channels along the *a*-axis, which are filled with $[CdCl_4]^{2-}$ anions and water molecules. The solvent water accessible volume of the channels is 1903.1 Å^3, about 38.3% of the total unit cell volume (4970.0 Å^3, estimated with Platon).[31]

It is interesting to compare the deformation degree of these three inclusion complexes. Normally, the Q[8] host is a relatively rigid macrocycle with centrosymmetric symmetry. However, all the Q[8] hosts in the inclusion complexes L-Val$_2$@Q[8], D-Leu$_2$@Q[8], and D-Met$_2$@Q[8] experience a significant deformation. As can be seen in Figure 8, for these three inclusion complexes, the largest and smallest O···O diameters of the Q[8] portals are in the ranges 10.721-11.064 Å and 8.879-9.850 Å, respectively. The deformation degree of the Q[8] host is related to the molecular size of the encapsulated guests. The deformation degree of the Q[8] host for these three inclusion complexes is in the order L-Val$_2$@Q[8] < D-Leu$_2$@Q[8] < D-Met$_2$@Q[8], because the molecular size of the encapsulated guests is in the order L-Val < D-Leu < D-Met.

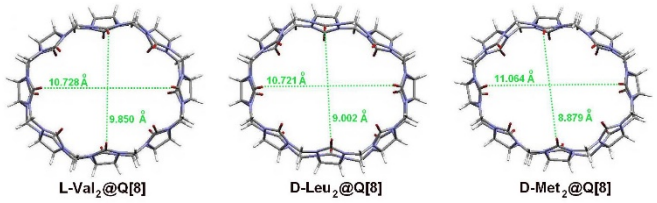

Figure 8. Comparison structures of distorted Q[8].

Experimental Section

Materials and methods:

The amino acid was commercially available and used as received. The Q[8] host was prepared according to a literature method.[32] All the ^{1}H NMR data were recorded on a JNM-ECZ400s MHz nuclear magnetic resonance (^{1}H NMR) spectrometer in D_2O at 293.15K. Elemental analyses (C, H, and N) were carried out on a PE 240C elemental analyzer.

ITC measurements. Microcalorimetric experiments were performed using an isothermal titration calorimeter Nano ITC (TA, USA). The heat evolved was recorded at 298.15 K. All solutions were degassed prior to titration experiments by sonication. 1.0×10^{-3} mol/L stock solution of amino acids and 1.0×10^{-4} mol/L stock solution of Q[8] were prepared in deionized water. A typical ITC titration was carried out by titrating the amino acid solution (1.0×10^{-3} mol/L) into a Q[8] solution. The concentration of Q[8] in the sample cell (1.3 mL) was 1.0×10^{-4} mol/L at pH=7. Computer simulations (curve fitting) were performed using the Nano ITC analyze software. First points in the ITC data are excluded when fitting the model to acquire the binding constant, enthalpy change, and entropy change.

Single-crystal X-ray crystallography:

Single-crystal data for the compounds **1** , **2** and **3** were collected on a Bruker D8 VENTURE diffractometer (for compounds **1** and **3**) and a Bruker Smart Apex CCD diffractometer (for compound **2**) with a graphite-monochromated Mo-Kα radiation source (λ = 0.71073 Å) respectively. 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 package,[33] respectively. 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. The SQUEEZE routine of Platon was employed for all compounds because of the disordered solvent water molecules.[34] A summary of crystal data, intensity measurements, structure solution, and refinement for all the three compounds are given in Table 1. CCDC 2122314, 2122315 and 2122316 contain 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.

Table 1. Crystal data as well as details of data collection and refinement for compounds **1**-**3**.

	1	**2**	**3**
Formula	$C_{58}H_{102}Cd_2Cl_8N_{34}O_{34}$	$C_{60}H_{105}Cd_2Cl_8N_{34}O_{34}$	$C_{53}H_{81}CdCl_4N_{33}O_{28}S$
M_r	2328.16	2355.20	1914.77
crystal system	monoclinic	monoclinic	triclinic
space group	$P2_1$	$P2_1$	$P1$
a (Å)	14.1506(13)	14.075(5)	17.535(6)
b (Å)	14.5033(14)	14.636(4)	17.696(7)
c (Å)	22.5841(17)	22.677(7)	18.620(7)
α (deg)	90	90	69.886(11)
β (deg)	90.460(3)	90.564(12)	78.459(12)
γ (deg)	90	90	66.732(11)
V (Å^3)	4634.8(7)	4671(3)	4970(3)
Z	2	2	2
*D*c (g·cm^{-3})	1.668	1.674	1.279
μ (mm^{-1})	0.789	0.784	0.428
F(000)	2383.0	2413.0	1972.0
Data/params	8630/568	11610/577	17211/1009
ϑ (deg)	2.28-28.30	2.30-28.12	2.32 -21.26
GOF(F^2)	1.007	1.003	1.011
R_1[$I>2(I)$]	0.0703	0.0697	0.1141
wR_2(all data)	0.2127	0.2364	0.3415
CCDC number	2122314	2122315	2122316

Preparation of compounds 1-3:

$(C_5H_{12}NO_2)^+_2$@Q[8]·2$[CdCl_4]^{2-}$·4$(H_3O)^+$·12H_2O (**1**)**:** L-Valine (20.3 mg, 0.18 mmol) and $CdCl_2$ 2.5H_2O (10.1 mg, 0.04 mmol) were added to an aqueous solution (3.0 ml, 6.0 M HCl) of Q[8] (10.0 mg, 0.0075 mmol). The mixture was stirred and heated at 70 °C for 10 min and then filtered. Slow solvent evaporation of the filtrate in air over a period of about two weeks provided suitable crystals of compound $C_{58}H_{102}Cd_2Cl_8N_{12}O_{34}$ (**1**) in about 26 % yield (based on Q[8]). Anal. Calcd for $C_{58}H_{102}Cd_2Cl_8N_{34}O_{34}$ (**1**): C, 34.49; H, 5.09; N, 8.32. Found: C, 35.03; H, 5.01; N, 8.27.

$(C_6H_{14}NO_2)^+_2$@Q[8]·2$[CdCl_4]^{2-}$·2$(H_3O)^+$·12H_2O **(2):** D-Leucine (20.2 mg, 0.15 mmol) and $CdCl_2$·2.5H_2O (10.1 mg, 0.04 mmol) were added to an aqueous solution (3.0 ml, 6.0 M HCl) of Q[8] (10.0 mg, 0.0075 mmol). The mixture was stirred and heated at 70 °C for 10 min and then filtered. Slow solvent evaporation of the filtrate in air over a period of about three weeks provided suitable crystals of compound **2**. The yield based on Q[8] is 40 %. Anal. Calcd for $C_{60}H_{105}Cd_2Cl_8N_{34}O_{34}$ (**2**): C, 35.21; H, 5.17; N, 8.21. Found: C, 34.97; H, 5.24; N, 8.32.

$(C_5H_{12}NO_2S)^+_2$@Q[8]·Q[8]·2$[CdCl_4]^{2-}$·2$(H_3O)^+$·18H_2O **(3):** D-Methionine (20.1 mg, 0.13 mmol) and $CdCl_2$·2.5H_2O (10.1 mg, 0.04 mmol) were added to an aqueous solution (3.0 ml, 6.0 M HCl) of Q[8] (10.0 mg, 0.0075 mmol). The mixture was stirred and heated at 70 °C for 10 min and then filtered. Slow solvent evaporation of the filtrate in air over a period of about two weeks provided suitable crystals of compound **3**. The yield based on Q[8] is 40 %. Anal. Calcd for $C_{53}H_{81}CdCl_4N_{33}O_{28}S$ (**3**): C, 40.33; H, 5.17; N, 7.99. Found: C, 39.98; H, 5.22; N, 8.04.

Conclusions

In conclusion, by using ^{1}H NMR spectroscopy and X-ray crystallography, we have demonstrated the capacity of the Q[8] host to recognize L-Valine, D-Leucine, and D-Methionine molecules, both in aqueous solution and in the solid state. NMR spectroscopic titration experiments revealed that the Q[8] host can encapsulate the L-Valine, D-Leucine, and D-Methionine molecules to form host-guest inclusion complexes in aqueous solution. We also successfully obtained single crystals of these three amino acids complexed with the Q[8] host. Their crystal structures unambiguously confirmed that the Q[8] host can accommodate two amino acid molecules with suitable size and shape. To accommodate different guests, the Q[8] host may experience a certain degree of deformation, which depends on the molecular size of the encapsulated guests.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21861011), the Innovation Program for High-level Talents of Guizhou Province (No. 2016-5657), "Chun-Hui" Fund of Chinese Ministry of Education (Z2017005, Z2015006). and the Natural Science Foundation of Anhui Province of China (1808085MB43, 2008085MB36). CR thanks the EPSRC for an Overseas Travel Grant (EP/R023816/1).

Notes and references

1 (a) M. Freidman, *J. Agric. Food Chem*., 1999, **47**, 3457-3479; (b) Y. Zhou and J. Yoon, *Chem. Soc. Rev*., 2012, **41**, 52-67; (c) H. Heli, M. Hajjizadeh, A. Jabbari and A. Moosavi-Movahedi, *Anal. Biochem*., 2009, **388**, 81-90; (d) Q. P. Duan, Y. Cao, Y. Li, X. Y. Hu, T. X. Xiao, C. Lin, Y. Pan and L. Y. Wang, *J. Am. Chem. Soc*., 2013, **135**, 10542-10549.

2 (a) B. B. Shi, K. C. Jie, Y. J. Zhou, J. Zhou, D. Y. Xia and F. H. Huang, *J. Am. Chem. Soc*., 2016, **138**, 80-83; (b) G. C. Yu, G. P. Tang and F. H. Huang, *J. Mater. Chem. C*., 2014, **2**, 6609-6617; (c) G. C. Yu, D. Wu, Y. Li, Z. H. Zhang, L. Shao, J. Zhou, Q. L. Hu, G. P. Tang and F. H. Huang, *Chem. Sci*., 2016, **7**, 3017-3024.

3 Y. Cao, X. Y. Hu, Y. Li, X. C. Zou, S. H. Xiong, C. Lin, Y. Z. Shen and L. Y. Wang, *J. Am. Chem. Soc*., 2014, **136**, 10762-10769.

4 (a) M. Liu, J. L. Kan, Y. Q. Yao, Y. Q Zhang, B. Bian, Z. Tao, Q. J. Zhu and X. Xiao, *Sensors & Actuators: B. Chem*., 2019, **283**, 290-297; (b) R. H. Gao, L. X. Chen, K. Chen, Z. Tao and X. Xiao, *Coord. Chem. Rev*., 2017, **348**, 1-24.

5 (a) Z. A. Wood, E. Schroder, J. R. Harris and L. B. Poole, *Trends Biochem. Sci*., 2003, **28**, 32-40; (b) Q. Zhang, D. Zhang, Y. Lu, G. Xu, Y. Yao, S. Li and Q. Liu, *Biosens. Bioelectron*., 2016, **77**, 963-970.

6 (a) C. B. Lebrilla, *Acc. Chem. Res*., 2001, **34**, 653-661; (b) W. Si, P. Xin, Z. T. Li and J. L. Hou, *Acc. Chem. Res*., 2015, **48**, 1612-1619; (c) A. Casnati, F. Sansone and R. Ungaro, *Acc. Chem. Res*., 2003, **36**, 246-254; (d) K. Yang, Y. Pei, J. Wen and Z. Pei, *Chem. Commun*., 2016, **52**, 9316; (e) M. Giuliani, I. Morbioli, F. Sansone and A. Casnati, *Chem. Commun*., 2015, **51**, 14140; (f) R. Pinalli, A. Pedrini and E. Dalcanale, *Chem. Soc. Rev*., 2018, **47**, 7006-7026.

7 (a) A. R. Urbach and V. Ramalingam, *Isr. J. Chem*., 2011, **51**, 664; (b) A. T. Wright, M. J. Griffin, Z. L. Zhong, S. C. McCleskey, E. V. Anslyn and J. T. McDevitt, *Angew. Chem. Int. Ed*., 2005, **44**, 6375.

8 (a) T. B. Wei, J. F. Chen, X. B. Cheng, H. Li, B. B. Han, Y. M. Zhang, H. Yao and Q. Lin, *Org. Chem. Front*., 2017, **4**, 210; (b) L. Chen, W. Si, L. Zhang, G. Tang, Z. T. Li and J. L. Hou, *J. Am. Chem. Soc*., 2013, **135**, 2152-2155; (c) S. Tashiro, M. Tominaga, M. Kawano, B. Therrien, T. Ozeki and M. Fujita, *J. Am. Chem. Soc*., 2005, **127**, 4546; (d) P. Wang, Z. T. Li and X. F. Ji, *Chem. Commun*., 2014, **50**, 13114-13116; (e) C. J. Li, J. W. Ma, L. Zhao, Y. Y. Zhang, Y. H. Yu, X. Y. Shu, J. Li and X. S. Jia, *Chem. Commun*., 2013, **49**, 1924-1926; (f) B. Hua, J. Zhou and G. C. Yu, *Tetrahedron Lett*., 2015, **56**, 986-989.

9 E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah and X. Lu, *RSC Adv*., 2012, **2**, 1213-1247.

10 X. L. Ni, X. Xiao, H. Cong, L. L. Liang, K. Chen, X. J. Cheng, N. N. Ji, Q.J. Zhu, S. F. Xue and Z. Tao, *Chem. Soc. Rev*., 2013, **42**, 9480-9508.

11 A. E. Kaifer, Acc. Chem. Res., 2014, **47**, 2160-2167.

12 K. I. Assaf and W. M. Nau, *Chem. Soc. Rev*., 2015, **44**, 394-418.

13 D. Shetty, J. K. Khedkar, K. M. Parkad and K. Kim, *Chem. Soc. Rev*., 2015, **44**, 8747-8761.

14 S. J. Barrow, S. Kasera, M. J. Rowland, J. Barrio and O. A. Scherman, *Chem. Rev*., 2015, **115**, 12320-12406.

15 (a) L. A. Logsdon, C. L. Schardon, V. Ramalingam, S. K. Kwee and A. R. Urbach, *J. Am. Chem. Soc*., 2011, **133**, 17087-17092; (b) J. M. Chinai, A. B. Taylor, L. M. Ryno, N. D. Hargreaves, C. A. Morris, P. J. Hart and A. R. Urbach, *J. Am. Chem. Soc*., 2011, **133**, 8810-8813; (c) L. A. Logsdon and A. R. Urbach, *J. Am. Chem. Soc*., 2013, **135**, 11414-11416; (d) L. C. Smith, D. G. Leach, B. E. Blaylock, O. A. Ali and A. R. Urbach, Sequence-

Specific, Nanomolar Peptide Binding via Cucurbit[8]uril-Induced Folding and Inclusion of Neighboring Side Chains. *J. Am. Chem. Soc*., 2015, **137**, 3663-3669.
16 (a) M. V. Rekharsky, H. Yamamura, Y. H. Ko, N. Selvapalam, K. Kim and Y. Inoue, *Chem. Commun*., 2008, 2236-2238; (b) W. J. Kim, K. Kim and H. I. Kim, *Angew. Chem*., 2014, **126**, 7591-7595; (c) J. W. Lee, H. H. L. Lee, Y. H. Ko, K. Kim and H. I. Kim, *J. Phys. Chem. B*, 2015, **119**, 4628-4636.
17 (a) A. Hennig, H. Bakirci and W. M. Nau, *Nat. Methods*, 2007, **4**, 629-632; (b) D. M. Bailey, A. Hennig, V. D. Uzunova and W. M. Nau, *Chem. Eur. J*., 2008, **14**, 6069-6077; (c) A. Praetorius, D. M. Bailey, T. Schwarzlose and W. M. Nau, *Org. Lett*., 2008, **10**, 4089-4092; (d) W. M. Nau, G. Ghale, A. Hennig, H. Bakirci and D. M. Bailey, Substrate-Selective Supramolecular Tandem Assays: Monitoring Enzyme Inhibition of Arginase and Diamine Oxidase by Fluorescent Dye Displacement from Calixarene and Cucurbituril Macrocycles. *J. Am. Chem. Soc*., 2009, **131**, 11558-11570.
18 M. Pozo, P. Hernàndez, L. Hernàndez and C. J. Quintana, *Mater. Chem*., 2011, **21**, 13657-13663.
19 S. Sonzini, T. J. S. Ryan and O. A. Scherman, *Chem. Commun*., 2013, **49**, 8779-8781.
20 M. A. Gamal-Eldin and D. H. Macartney, *Org. Biomol. Chem*., 2013, **11**, 488-495.
21 T. Minami, N. A. Esipenko, B. Zhang, L. Isaacs and P. Anzenbacher, *Chem. Commun*., 2014, **50**, 61-63.
22 Y. He, Y. Liang and H. Yu, *ACS Comb. Sci*., 2015, **17**, 409-412.
23 (a) D. T. Dang, H. D. Nguyen, M. Merkx and L. Brunsveld, *Angew. Chem. Int. Ed*., 2013, **52**, 2915-2919. (b) H. D. Nguyen, D. T. Dang, J. L. J. van Dongen and L. Brunsveld, *Angew. Chem., Int. Ed*., 2010, **49**, 895-898.
24 O. Danylyuk and V. P. Fedin, *Cryst. Growth Des*., 2012, **12**, 550-555.
25 (a) P. Thuéry, *Inorg. Chem*., 2011, **50**, 10558-10560; (b) P. Thuéry, *CrystEngComm*, 2012, **14**, 8128-8136.
26 (a) J. M. Yi, Y. Q. Zhang, H. Cong, S. F. Xue and Z. Tao, *J. Mol. Struct*., 2009, **933**, 112-117.
27 (a) P. H. Shan, S. C. Tu, R. L. Lin, Z. Tao, J. X. Liu and X. Xiao, *CrystEngComm*, 2017, **19**, 2168-2171; (b) P. H. Shan, R. L. Lin, M. Liu, Z. Tao, X. Xiao and J. X. Liu, *Chin. Chem. Lett*., 2021, **32**, 2301-2304; (c) P. H. Shan, J. Zhao, X. Y. Deng, R. L. Lin, B. Bian, Z. Tao, X. Xiao and J. X. Liu, *Anal. Chim. Acta*., 2020, **1104**, 164-171.
28 Y. H. Ko, E. Kim, I. Hwang and K. Kim, *Chem. Commun*., 2007, 1305-1315.
29 (a) E. L. Lin, G. S. Fang, W. Q. Sun and J. X. Liu, *Scientific Reports*, 2016, **6**, 39057; (b) G. S. Fang, W. Q. Sun, W. X. Zhao, R. L. Lin, Z. Tao and J. X. Liu, *Org. Biomol. Chem*., 2016, **14**, 674-679; (c) R. L. Lin, J. Q. Li, J. X. Liu and A. E. Kaifer, *J. Org. Chem*., 2015, **80**, 10505-10511.
30 (a) X. L. Ni, X. Xiao, H. Cong, Q. J. Zhu, S. F. Xue and Z. Tao, *Acc. Chem. Res*., 2014, **47**, 1386-1395; (b) R. L. Lin, Y. P. Dong, M. Tang, Z. Liu, Z. Tao and J. X. Liu, *Inorg. Chem*., 2020, **59**, 3850-3855.
31 A. L. Spek, PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, 1998.
32 (a) A. Day, A. P. Arnold, R. J. Blanch and B. J. Snushall, *Org. Chem*., 2001, **66**, 8094-8100; (b) J. Kim, I. S. Jung, S. Y. Kim, E. Lee, J. K. Kang, S. Sakamoto, K. Yamaguchi and K. J. Kim, New Cucurbituril Homologues: Syntheses, Isolation, Characterization, and X-ray Crystal Structures of Cucurbit[*n*]uril (*n* = 5, 7, and 8). *J. Am. Chem. Soc*., 2000, 122, 540-541.
33 (a) G. M. Sheldrick, SHELXS-97, Program for X-ray Crystal Structure Determination, University of Göttingen, Germany, 1997; (b) G. M. Sheldrick, SHELXL-97, Program for X-ray Crystal Structure Refinement, University of Göttingen, Germany, 1997; (c) G, M. Sheldrick, *Acta Crystallogr. Sect. A*, 2008, **64**, 112.
34 A. L. Spek, *J. Appl. Crystallogr*., 2003, **36**, 7.

