J Incl Phenom Macrocycl Chem (2009) 64:325–329
DOI 10.1007/s10847-009-9571-4

ORIGINAL ARTICLE

A novel 1:2 cucurbit[8]uril inclusion complex with *N*-phenylpiperazine hydrochloride

Xiaojun Wu · Xianggao Meng · Gongzhen Cheng

Received: 6 January 2009 / Accepted: 12 March 2009 / Published online: 25 March 2009

Abstract A new 1:2 inclusion complex of cucurbit[8]uril (CB[8]) and protonated *N*-phenylpiperazine was synthesized and characterized by ^{1}H NMR and X-ray crystallography. The crystal structure showed that the phenyl rings of the two equivalents of guest encapsulated in the cavity of CB[8] are parallel to one another with a mean plane separation of 3.899 Å. In contrast, the piperazinyl phenyl ammonium moieties slightly protrude from the ureidyl carbonyl lined portals in order to accommodate the ion–dipole interaction between host and guest which provides a substantial driving force for the assembly. The oxygen atoms of the carbonyl groups form hydrogen bonds with the hydrogen atoms in both bridging methylene groups of CB[8] and water molecules. There are also hydrogen bonds formed among CB[8], water, and the protonated piperazinyl rings. These hydrogen bonds are formed between the ureidyl C=O groups and hydrogens in methylenes of piperazinyl rings; through hydrogen bonding N^+–H···O(H)–H···O=C. The protonated piperazinyl rings connect the carbonyl groups with the bridging water molecules.

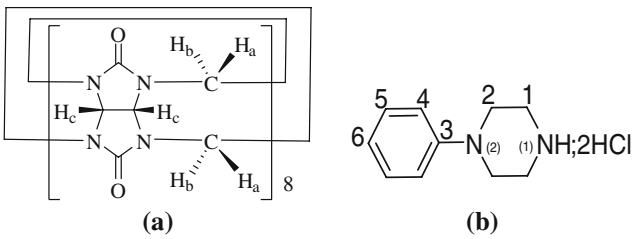
Keywords Cucurbit[8]uril · Phenylpiperazine · Inclusion complex · Crystal structure · NMR

X. Wu (✉) · G. Cheng
College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, People's Republic of China
e-mail: xjwuwuda@yahoo.com.cn

X. Meng
College of Chemistry, Central China Normal University, Wuhan 430079, People's Republic of China

Introduction

Cucurbit[8]uril (CB[8]) has attracted much attention since it was discovered and separated successfully by Kim et al. [1]. CB[8] has a rigid, pumpkin-like structure with a cavity volume of 479 Å^3 which is substantially larger than those of the smaller homologues (CB[*n*], $n = 5$–7). In particular, the pioneering work of Kim has shown that CB[8] is capable of binding to two guests simultaneously to form *ternary complexes* [2–6]. For example, CB[8] can from a 1:2 host–guest homomeric complex with protonated 2,6-bis(4,5-dihydro-1H-imidazol-2-yl) naphthalene (BDIN) as determined by X-ray crystallography [1]. Even more impressively, CB[8] can also form a 1:1:1 heteroguest ternary complex with electron-deficient (i.e. methylviologen, MV^{2+} and its derivative) and electron-rich guests (i.e. 2,6-dihydroxynaphthalene and 1,4-dihydroxybenzene). The selective inclusion of the hetero-guest pairs is driven by charge-transfer interactions as evidenced by UV–visible spectroscopy [7, 8]. Moreover, a guest that consists of both electron-rich and electron-deficient units connected by a suitable spacer group can form 1:1 and 2:2 inclusion complexes of CB[8] through host-induced charge-transfer interactions [9–11]. Before then Kim and co-workers reported that the 1:1 inclusion complex of MV^{2+}-CB[8] can even be completely and reversibly convert to the 2:1 complex of $(MV^{+\bullet})_2$-CB[8] upon one-electron reduction of the guest [12]. Besides the aromatic ammoniums, alkyl ammoniums can be encapsulated in CB[8] in a U-shaped conformation of the alkyl chains as reported by Kim and co-workers very recently [13]. Furthermore, CB[8] can form inclusion complexes with organometallic compounds, for example, a stable 1:1 inclusion complex of $Ru(bpy)_3$-MV^{2+} and CB[8] [14], and a 1:1 inclusion complex of CB[8] and the anti-cancer dinuclear platinum complex



Scheme 1 The molecular structures **a** the host CB[8] and **b** the guest *N*-phenylpiperazine hydrochloride

trans-[{PtCl(NH_3)$_2$}$_2$(μ-$NH_2(CH_2)_8NH_2$)]$^{2+}$ were developed [15]. As a result of its wide array of impressive binding and inclusion properties, CB[8] has potential application in several fields [6]. As a first step toward the development of CB[8] for controllable drug delivery applications we decided to study the inclusion properties of CB[8] toward *N*-phenylpiperazine hydrochloride. In this paper, we report the synthesis and crystal structure of the 1:2 inclusion complex of CB[8] and phenyl piperazine hydrochloride (Scheme 1). This result stands in contract to the work of Tao and co-workers who have shown that a mixture of 1:1 and 1:2 complexes is formed between CB[8] and a substituted benzyl piperazine as evidenced by NMR spectroscopy [16].

Experimental

General

Cucurbit[8]uril was prepared and purified as described in the literature [17]. *N*-phenylpiperazine hydrochloride was commercially available and used as received. ^{1}H and ^{13}C NMR spectra were collected on a Varian INOVA-600 spectrometer. MALDI-TOF mass spectra were recorded on a Voyager DE STR MALDI-TOF instrument.

Preparation of 1:2 CB[8] inclusion complex with phenylpiperazine hydrochloride

A mixture of CB[8] (18.5 mg, 0.13 mmol) and *N*-phenylpiperazine hydrochloride (51.2 mg, 2.6 mmol) in 30 mL of distilled water was heated on a water bath at 100 °C for 3 h. After filtration a clear solution was obtained which was concentrated to about 8 mL and then was cooled to room temperature. Colorless crystals were obtained after storing the solution in a refrigerator at 5 ± 1 °C for 7–10 days. Single crystals suitable for X-ray diffraction were chosen from this material. The residue was filtered to afford some crystals that were washed with iced water and dried under vacuum at lower temperature. Yield: 3.9 mg, 12%. Elemental analysis calculation for inclusion complex based on X-ray crystal data, empirical formula: $(C_{48}H_{48}N_{32}O_{16}) \cdot 2[(C_{10}H_{16}N_2)^{2+} \cdot 2Cl^-] \cdot 4HCl \cdot 31H_2O$; $M_f = 2503.81$, Calc(%): C, 32.63; H, 5.83; N 20.14. Found(%): C, 32.73; H, 5.72; N, 20.03. ^{1}HNMR (600 MHz, D_2O): δ 2.97 (s, 2H, NH), 3.40 (s, 8H, C(2)H), 3.55 (s, 8H, C(1)H), 3.88 (d, 16H, ^2J = 15 Hz, Hb), 5.20 (s, 16H, H_C), 5.35 (d, 16H, ^2J = 15 Hz, Ha), 6.10–6.25 (m, 10H, Phenyl). ^{13}CNMR (150 MHz, D_2O): δ 41.2 (C1), 51.7 (C2), 53.8 (CH_2 in CB[8]), 72.0 (CH in CB[8]), 102.3 (C4), 119.6 (C6), 129.1 (C5), 156.6 (C=O in CB[8]), 158.5 (C3). MS(MALDI-TOF): m/z(%) 1492.3245(100, CB[8] · [($C_{10}H_{14}N_2$)+2H$^+$]), 164.1255(100, [($C_{10}H_{14}N_2$)+2H$^+$]).

Crystal structure determination

The data collections were performed on a Bruker SMART APEX CCD diffractometer, with a graphite monochromatized MoKα radiation (λ = 0.71073 Å) at 200 K in the range of $1.5 < \theta < 25.0$. Structural solution and full matrix least-squares refinements based on F^2 were performed with

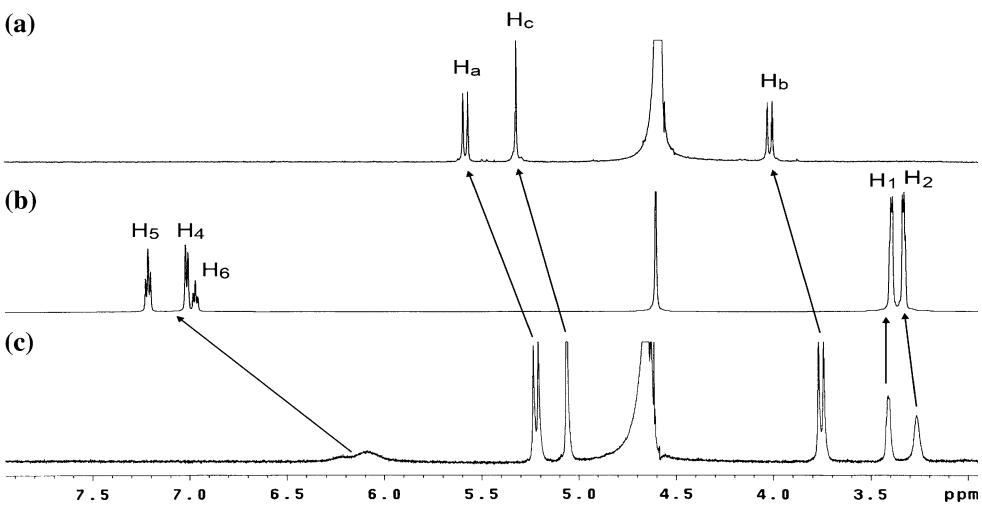


Fig. 1 ^{1}H NMR spectra recorded in D_2O for: (a) the host molecule CB[8], (b) the guest molecule phenylpiperazine, and (c) the 1:2 inclusion complex

the SHELXS-97 and SHELXL-97 program package [18, 19], respectively.

Result and discussion

^{1}H NMR Spectroscopy of the CB[8] · Phenylpiperazine ammonium ion inclusion complex. In spite of the poor solubility of CB[8] in water (<0.01 mM) [2], D_2O was chosen as the solvent for the NMR studies. Figure 1 shows the ^{1}H NMR spectra of CB[8], *N*-phenylpiperazine hydrochloride, and the 1:2 inclusion complex. On the basis of the integrals of the protons for guest versus the integral of protons for solubilized host, it was determined that the complex was formed in a host:guest ratio of 1:2. It can be clearly seen that the protons of both host and guest undergo substantial up-field shifting as a result of inclusion complexation. Most significant are the observed chemical shift changes for H4, H5 and H6 on phenyl ring which are close to 1 ppm. Furthermore, the protons H4–H6 appear as broadened multiplets at 6.0–6.3 ppm which suggests that the phenyl rings are encapsulated inside the cavity of CB[8] and some degree of motional restriction of phenyl rings arising from the inclusion and the π–π stacking interaction between the phenyl rings.

Additionally, the protons in N(2) of piperazinyl ring gave a bigger chemical shift displacement ($\Delta\delta$H(2)1.13 ppm) than those in N(1)($\Delta\delta$H(1)1.05 ppm),indicating there may be the ion–dipole interactions between NH^+ cations and the carbonyl portals of CB[8] other than NH_2^+ cations. As illustrated in Fig. 2, the Job's plots showed the minima at $\chi = 0.6$ for the protons H1, H2, H_a, H_b, and H_c which indicates the formation of the complex with a 1:2 stoichiometry, which was in agreement with the result of X-ray crystallography.

All these results suggest that CB[8] and *N*-phenylpiperizine hydrochloride form a complex with 1:2 stoichiometry, phenyl rings be encapsulated in the cavity of the host interacting through π–π stacking. The piperazinyl rings protrude from the carbonyl portals in order to satisfy the geometric requirements of the ion–dipole interactions between NH^+ cations and the C=O groups.

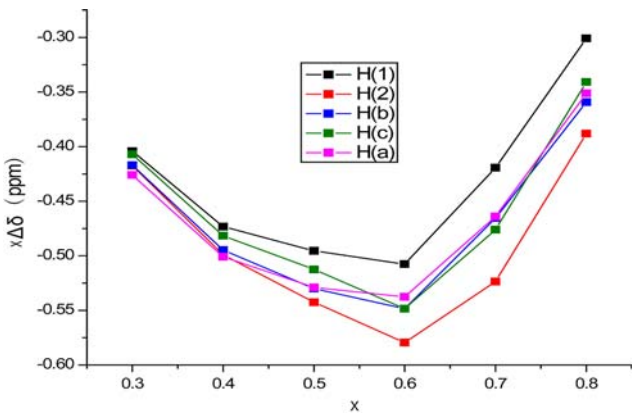


Fig. 2 Job's plot for H(1), H(2), H(a), H(b) and H(c)

X-ray crystallography of 1:2 CB[8] inclusion complex with phenylpiperazine hydrochloride

A summary of the crystallographic data, data collection and refinements for the title inclusion complex is given in Table 1. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center with deposition number CCDC 695460.

Table 1 The crystal data of inclusion complex

Empirical formula	$(C_{48}H_{48}N_{32}O_{16}) \cdot 2[(C_{10}H_{16}N_2)^{2+} \cdot 2Cl^-] \cdot 4HCl \cdot 31H_2O$
Formula weight	2503.81
Temperature (K)	200
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P2(1)/c (No. 14)
Unit cell dimensions	a (Å) = 13.9997 (8), α (deg) = 90 b (Å) = 17.7743 (10), β (deg) = 96.038 (1) c (Å) = 22.3019 (13), γ (deg) = 90
Volume (Å^3)	5518.7(5)
Z	2
Density(calculated) (Mg m^{-3})	1.507
Absorption coefficient (mm^{-1})	0.309
F(000)	2636
Crystal size (mm)	0.10 × 0.10 × 0.20
Theta range for data collection (deg)	1.5–25.00
Index ranges	$-16 \le h \le 16$, $-12 \le k \le 21$, $-26 \le l \le 26$
Reflections collected	31429
Independent reflections	9662 [R(int) = 0.085]
Completeness to theta = 25.00°	99.3%
Absorption correction	Multi-scan
Max and min transmission	0.9697 and 0.9318
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	9662/5/485
Goodness-of-fit on F^2	1.00
Final R indices [I > 2$_\sigma$(I)]	$R_1 = 0.0772$, $wR_2 = 0.2113$
R indices (all data)	$R_1 = 0.1050$, $wR_2 = 0.2277$
Largest diff peak and hole (eÅ^{-3})	1.349 and −0.641

As shown in Fig. 3, the encapsulated phenyl rings in the cavity of CB[8] are parallel with a plane separation of 3.899 Å (centroid to centroid distance) indicating a π–π stacking of the two rings. The piperazinyl rings adopt chair conformations and interact with carbonyl portals of CB[8] by the ammonium cations $N^+H\cdots O{=}C$ H-bonds and ion–dipole interactions. As such, in the inclusion complex, only the phenyl rings are included inside the cavity with the piperazinyl rings protruding from the carbonyl-rimmed portals. The combined driving force of π–π interactions and NH···O=C H-bonds in the conformation in which the two phenyl rings are included in the cavity are better than the driving force for inclusion of one phenyl and one piperazinyl group or two piperazinyl groups.

There are various hydrogen bonds in the solid state of the complex. The critical parameters for the hydrogen bonds between the hydrogens H_a and H_b of the bridging methylenes of CB[8] and carbonyl oxygens reveal that the C–H···O distances range from 2.854–2.912 Å. The critical parameters for the hydrogen bonding interactions between water molecules and the ureidyl C=O groups of CB[8] reveal that the O–H···O distances fall in the range 2.699–3.020 Å.

Furthermore, hydrogen bonding played an important role in connecting the hosts and the guests as shown in Fig. 3. These hydrogen bonds mainly consist of interactions between carbonyl oxygens and methylene hydrogens of the piperazine rings with the C–H…O distances of 3.206, 3.367 and 3.418 Å and water-bridging hydrogen bonds, i.e. hydrogen bonds of hydrogens in N(2) of piperaziniums with oxygens of water molecules, of which hydrogens connect with carbonyl oxygens through hydrogen bonding model of C=O···H–O. The distance of N^+–H…O is 2.671 Å, and the distance of O–H…O(=C) is 2.764 Å.

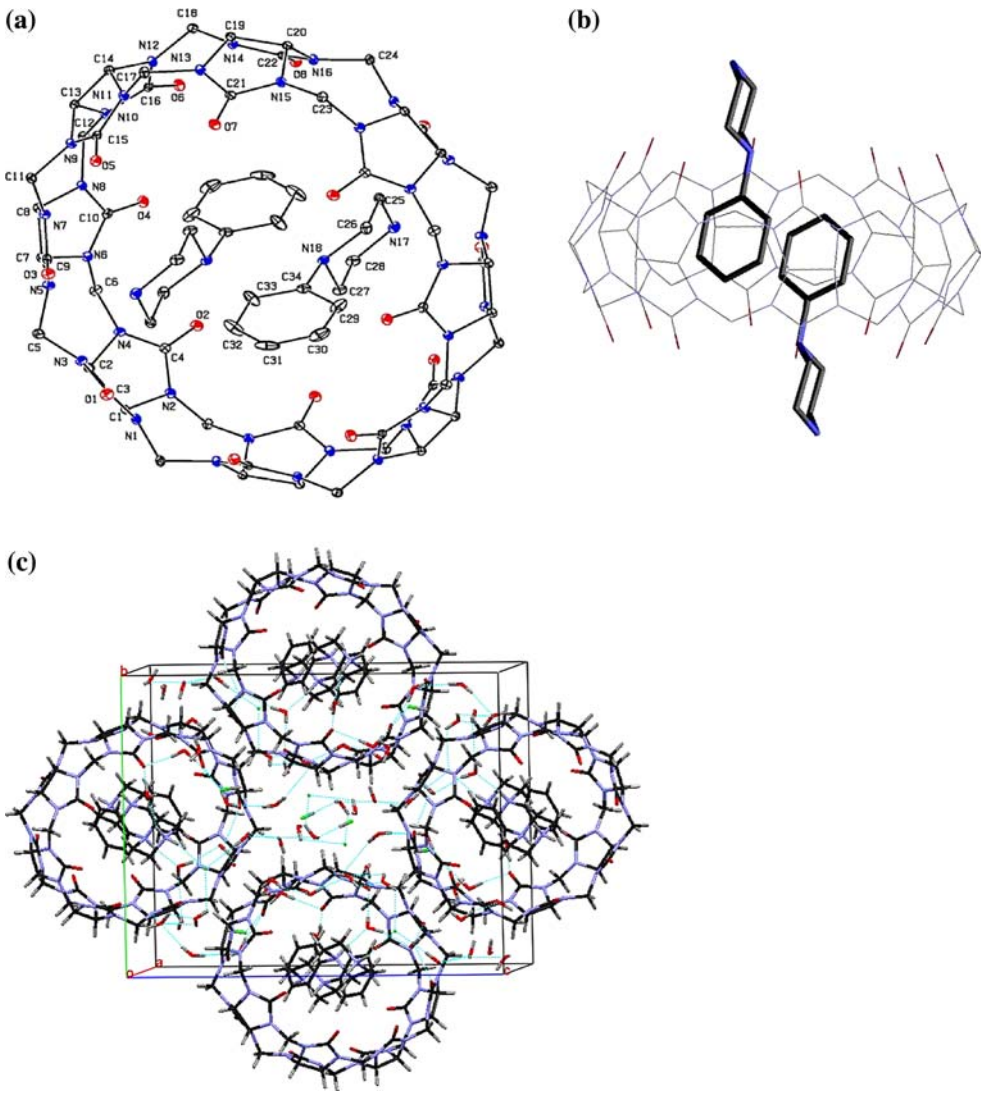


Fig. 3 X-ray crystal structure of 1:2 CB[8] inclusion complex with phenylpiperazine hydrochloride; **a** top view, **b** side view and **c** packing diagram of inclusion complex. Color code: Oxygen: red, nitrogen: blue, carbon: gray

Conclusions

Cucurbit[8]uril and *N*-phenylpiperazine hydrochloride formed a 1:2 inclusion complex, the stoichiometry was confirmed by NMR spectroscopy and determined by X-ray crystallography. The two encapsulated phenyl rings are parallel and interact by π–π stacking interactions. The piperazinyl rings protrude from the carbonyl portals and connect with ureidyl C=O groups through ion–dipole interactions, hydrogen bonds of methylene hydrogens with carbonyl oxygens, and water-bridging hydrogen bonds. All these interactions, i.e. π–π stacking, ion–dipole interactions and hydrogen bonding, between CB[8] and *N*-phenylpiperaziniums make the 1:2 inclusion complex very stable.

Acknowledgement This work was financially supported by National Natural Science Foundation of China (No. 20572083).

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