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Encapsulation of haloalkane 1-(3-Chlorophenyl)-4-(3-chloropropyl)-piperazinium in symmetrical α,α',δ,δ'-tetramethyl-cucurbit[6]uril

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Complexation of haloalkane 1-(3-Chlorophenyl)-4-(3-chloropropyl)-piperazinium (PZ^+) dihydrochloride with symmetrical α,α',δ,δ'-tetramethyl-cucurbit[6]uril (TMeQ[6]) has been investigated using NMR spectroscopy, MALDI-TOF mass spectrometry, isothermal titration calorimetry (ITC), and X-ray crystallography. Our data indicate that the chloropropyl group of PZ^+ resides within the cavity of TMeQ[6] in both aqueous solution and solid state, generating highly stable inclusion complex PZ^+@TMeQ[6]. In aqueous solution, the formation of inclusion complex PZ^+@TMeQ[6] benefits from the ion−dipole interactions between the guest PZ^+ and the host TMeQ[6]. While in solid state, hydrogen−bonding interactions also play an important role in stabilizing the inclusion complex PZ^+@TMeQ[6].

In the past few decades, encapsulation of molecules and ions (including cations and anions) in the intramolecular cavities of cavitands, such as cyclodextrins, calixarenes, cyclophanes, pillar[n]arenes, and self-assembling capsules is well documented.[1-3] Haloalkanes are of wide interest chemical compounds because they are important synthetic intermediates/reagents for organic reactions and widely used as fire extinguishants, refrigerants, propellants, and pharmaceuticals. So the recognition and encapsulation of haloalkanes is considered to be important in supramolecular chemistry. However, very few reports on haloalkanes encapsulating in a cavitand have been demonstrated in the literature.[4,5] Very recently, Jovica D. Badjić et al demenstrated the encapsulation of tetrahedral haloalkanes within gated molecular baskets through computational and experimental studies.[4] Julius Rebek, Jr. et al found that longer n-halides and α,ω-dihalides C_7–C_{11} are bound within some water-soluble deep cavitands and display unusual orientation and reactivity.[5]

As one kind of unique macrocyclic cavitands, cucurbit[n]urils (n = 5–8, 10, abbreviated as Q[*n*]) and their derivatives possess a hydrophobic cavity that can accommodate suitable organic molecules through hydrophobic interactions.[6,7] In the past decade, a variety of guest molecules like aromatic compounds, alkanes and alcohols have been reported to be bound into the hydrophobic cavities of Q[*n*]s in appropriate condition. It is therefore of interest to ask whether the hydrophobic cavity of Q[*n*]s could be exploited to encapsulate haloalkanes. In order to address this question, we prepared the haloalkane 1-(3-Chlorophenyl)-4-(3-chloropropyl)-piperazinium (PZ^+, Fig. 1) hydrochloride as guest molecule. On the other hand, symmetrical α,α',δ,δ'-tetramethyl-cucurbit[6]uril[8] (TMeQ[6], Fig. 1), a derivative of Q[6] previously designed and synthesized in our laboratory, was chosen as host molecule. In the present work, we demonstrate the binding behaviours of guest PZ^+ with host TMeQ[6] in both solution and solid states by using NMR spectroscopy, MALDI-TOF mass spectrometry, X-ray crystallography and isothermal titration calorimetry (ITC).

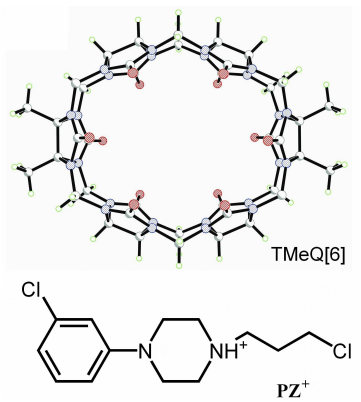

Fig. 1 Structures of the host and guest used in this work.

Materials and methods: 1-(3-Chlorophenyl)-4-(3-chloropropyl)-piperazine was purchased from Aldrich and used as supplied without further purification. TMeQ[6][8] was prepared according to a literature method. All the NMR data were recorded on a Bruker DPX 400 spectrometer in D_2O. MALDI-TOF mass spectrometry was performed with a Bruker

BIFLEX III ultra-high resolution Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer with α-cyano-4-hydroxycinnamic acid as matrix.

Single-crystal X-ray crystallography: Single crystals of complex 1 were grown from water by slow evaporation. Diffraction data of complex 1 were collected at 273(2) K with a Bruker SMART Apex-II CCD diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Empirical absorption corrections were performed 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, respectively.[9] Non-hydrogen atoms were treated anisotropically in all cases. All hydrogen atoms were introduced as riding atoms with an isotropic displacement parameter equal to 1.2 times that of the parent atom.

Crystal data for complex 1: $[(C_{13}H_{19}N_2Cl_2)^+@(C_{40}H_{44}N_{24}O_{12})]\cdot 10(H_2O)\cdot Cl^-$, Mr = 1580.85, monoclinic, space group $P2_1$, a = 14.6268(2) Å, b = 18.3253(3) Å, c = 15.3798(2) Å, β = 118.0110(10)°, V = 3639.50(9) Å^3, Z = 2, Dc = 1.443 g cm^{-3}, $F(000)$ = 1664, GOF = 1.030, R_1 = 0.0850 ($I>2\sigma(I)$), wR_2 = 0.2391 (all data). CCDC 1039248 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.

Preparation of complex 1: To a solution of 1-(3-Chlorophenyl)-4-(3-chloropropyl)-piperazinium hydrochloride (17.5 mg, 0.050 mmol) in 10 mL H_2O, TMeQ[6] (5.3 mg, 0.005 mmol) was added. The resulting reaction mixture was stirred for 5 min at 50 °C and filtered. Slow solvent evaporation of the filtrate in air over a period of about three weeks provided rhombic colorless crystals of complex 1 with the yield of 1.4 mg (20%). Anal. Calcd for $C_{53}H_{89}N_{26}O_{24}Cl_3$: C, 40.27; H, 5.67; N, 23.04. Found: C, 40.22; H, 5.54; N, 23.07.

Isothermal titration calorimetry (ITC) experiments: The association constants and thermodynamic parameters for the inclusion complexation of PZ^+ guest with TMeQ[6] host were determined by titration calorimetry with a Nano ITC instrument (TA, USA) in 10 mM sodium phosphate buffer (pH = 7.0). An aqueous solution (0.1 mm) of TMeQ[6] was placed in the sample cell (1.3 mL). As a solution (1 mm) of the guest PZ^+ was added in a series of 25 injections (10 μL), the heat evolved was recorded at T = 298.15 K. The heat of dilution was corrected by injecting the guest solution into deionized water and subtracting these data from those of the host – guest titration. Computer simulations (curve fitting) were performed using the Nano ITC analyze software.

Fig. 2 shows the ^{1}H NMR spectra of guest PZ^+ in the absence and presence of 0.68, 1.00 equivalent of TMeQ[6] in neutral D_2O solution. In the presence of 1.00 equiv of TMeQ[6], the resonances for α, β and γ protons of the guest PZ^+ shifted upfield by 0.96, 0.83 and 0.63 ppm, respectively, from those of the free guest PZ^+, indicative of their positioning within the cavity of TMeQ[6]. In contrast, the resonances of piperazinium protons undergo an obvious downfield shift ($\Delta\delta$ in the range of 0.08 ~ 0.78 ppm), indicating the piperazinium moiety is situated outside the portal of the TMeQ[6]. On the other hand, when the guest/host ratio is larger than 1:1, only the signals of the complexed guest were observed, suggesting that the exchange rate between the free guest and the TMeQ[6]-complexed guest is fast on the NMR time scale. In summary, based on the ^{1}H NMR spectra we conclude that the chloropropyl moiety of the PZ^+ guest was encapsulated into the cavity of the TMeQ[6] host, generating a 1:1 host–guest inclusion complex $PZ^+@$TMeQ[6]. Apparently, the major driving force for the complexation behavior in aqueous solution appears to be the ion–dipole interactions between the protonated nitrogens in the PZ^+ and the carbonyl oxygens at the portals of the TMeQ[6].

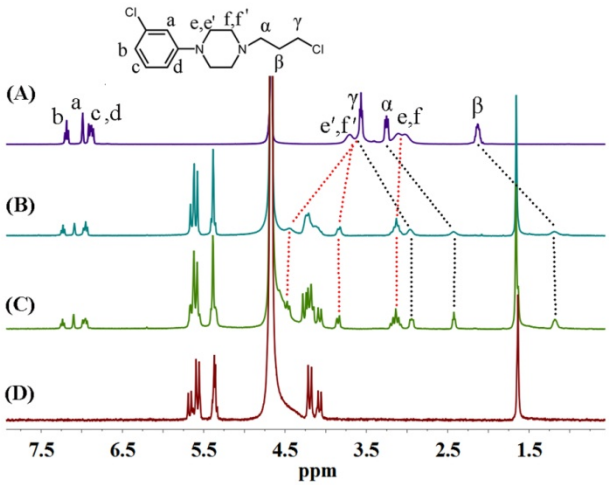

Fig. 2 ^{1}H NMR spectra of 3.5 mg PZ^+ in absence (a) and presence of 0.67 (b), and 1.0 (c) equiv of TMeQ[6] in 0.50 ml D_2O at 293 K. (d) shows the 1H NMR spectrum of TMeQ[6] in 0.50 mL D_2O at 293 K.

Moreover, 2-D diffusion-ordered NMR spectroscopy (DOSY) experiments were performed to afford further evidence for the formation of 1:1 inclusion complex $PZ^+@$TMeQ[6]. Fig. 3 depicts the DOSY spectra of the above host-guest system in D_2O at 298 K. It is evident from the spectra that all the peaks correlated to the signals in the chemical shift dimensions are in a horizontal line. As a consequence, all the proton signals, due to the host and the guest, display the same diffusion co-efficient ($D = 2.69 \times 10^{-10}$ m^2 s^{-1}) indicating that they are parts of the same species. The 1:1 stoichiometry of the inclusion complex $PZ^+@$TMeQ[6] was also established by the MALDI-TOF spectrum (Fig. 4), which showed the singly charged peak at m/z = 1326.79 for the inclusion complex $PZ^+@$TMeQ[6] (calculated for $[(C_{13}H_{19}N_2Cl_2)^+@(C_{40}H_{44}N_{24}O_{12})]$, 1325.45).

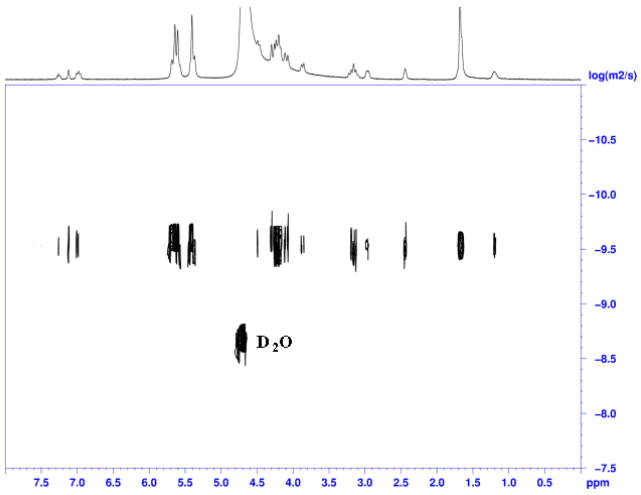

Fig. 3 DOSY spectra of the inclusion complex PZ^+@TMeQ[6] in D_2O at 298 K.

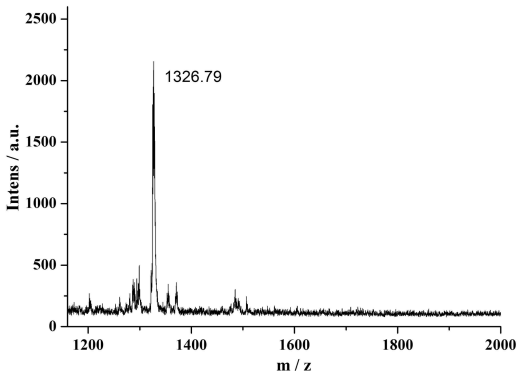

Fig. 4 MALDI-TOF mass spectrum of inclusion complex PZ^+@TMeQ[6].

After observing the complexation behaviour of the inclusion complex PZ^+@TMeQ[6] by NMR spectroscopy, we attempted to obtain solid-state evidence. Slowly evaporating the aqueous solution of the host TMeQ[6] and the guest PZ^+ in 1:1 ratio yielded single crystals of complex **1**, $[(C_{13}H_{19}N_2Cl_2)^+@(C_{40}H_{44}N_{24}O_{12})]\cdot 12(H_2O)\cdot Cl^-$. The single-crystal structural analysis reveals that the complex **1** crystallizes in the monoclinic crystal system, chiral space group $P2_1$. As can be seen in Fig. 5, the chloropropyl moiety of the PZ^+ guest is located inside the cavity of the TMeQ[6] host, while the piperazinium group and the chlorophenyl group remain outside of the portal of the TMeQ[6] host, which is in agreement with what we have observed in the aqueous solution by ^1H NMR spectroscopy. It is interesting to note that the encapsulated guest PZ^+ forms strong hydrogen−bonding with the host TMeQ[6]: N(26)–H···O(3) 2.881(5) Å, N(26)–H···O(2) 2.881(5) Å. Accordingly, in addition to the ion–dipole interactions, the hydrogen−bonding interactions also contribute to the formation of the inclusion complex PZ^+@TMeQ[6]. In the crystal structure of the complex 1, each inclusion complex PZ^+@TMeQ[6] is surrounded by numerous water molecules and chloride anions, and they interact to form a complicated hydrogen-bonding network.

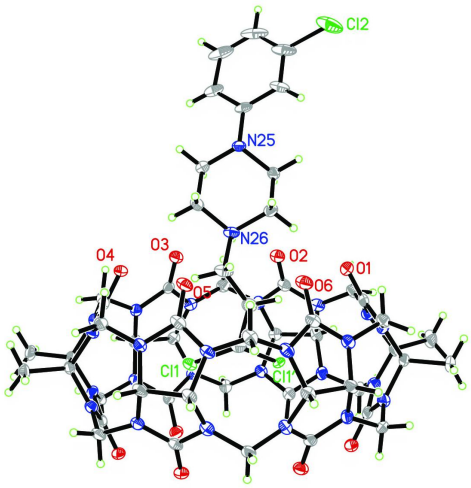

Fig. 5 ORTEP diagram of the inclusion complex PZ^+@TMeQ[6]; displacement ellipsoids are drawn at the 30% probability level. Solvate water molecules and chloride anions are omitted for clarity. O = red, C = grey, N = light blue and Cl = green.

Isothermal titration calorimetry (ITC) was used to quantify the binding constant (*K*a), and also the thermodynamic parameters ΔG^o, ΔH^o, $T\Delta S^o$ for the encapsulation of the PZ^+ guest by the TMeQ[6] host. The binding constant (*K*a) for the complexation of the PZ^+ guest with TMeQ[6] host was determined to be 1.43×10^6 M^{-1} at 298.15 K, which is much larger than that of previous reported other haloalkanes with other cavitands.[3] From the ΔH^o and $T\Delta S^o$ values in the Fig. 6, it is clear that the formation of the inclusion complex PZ^+@TMeQ[6] is enthalpically driven. The observed negative enthalpy change (ΔH^o = -38.96 kJ·mol^{-1}) is most probably due to the contribution of ion dipole interactions between the protonated nitrogen atoms in the PZ^+ and the carbonyl oxygens

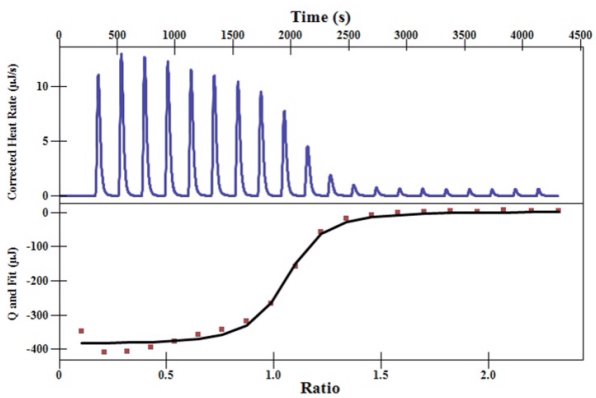

Fig. 6 ITC profile of host TMeQ[6] with guest PZ^+ at 298.15 K: K_a = 1.43×10^6 M^{-1}, ΔG^o = -35.14 kJ·mol^{-1}, ΔH^o = -38.96 kJ·mol^{-1}, $T\Delta S^o$ = -3.82 kJ·mol^{-1}.

at the portals of the TMeQ[6]. The adverse negative entropy ($T\Delta S^o$ = -3.82 kJ·mol^{-1}) arises possibly from the restriction of the guest molecule.

Conclusions

In summary, we have discovered that that the TMeQ[6] host have the ability to encapsulate haloalkane guest PZ^+ in both aqueous solution and solid state. To the best of our knowledge, this is the first example of haloalkanes encapsulated inside the cavities of Q[*n*]s which has been unequivocally characterized by NMR spectroscopy, isothermal titration calorimetry and X-ray crystallography. Our studies indicate that the driving force of the formation of the highly stable inclusion complex PZ^+@TMeQ[6] is the ion–dipole interactions between the guest and the host, and also the hydrogen−bonding interactions in solid state. We are currently investigating the possibility of other haloalkanes encapsulated by other Q[*n*]s.

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Notes and references

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