Host–Guest Chemistry

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U-Shaped Conformation of Alkyl Chains Bound to a Synthetic Host**

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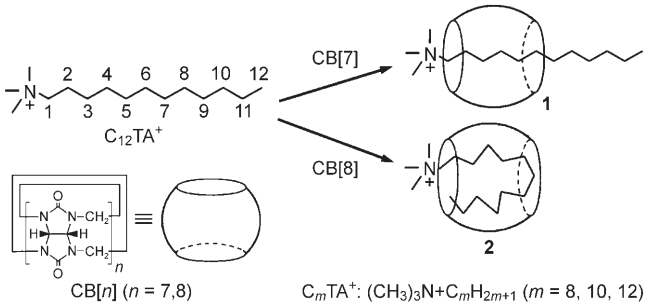
Long-chain fatty acids play important roles in cellular metabolism both as metabolic fuels and also as building blocks for membrane-forming complex lipids. Fatty acid binding proteins (FABPs) involved in the transport and metabolism of fatty acids have distinct binding preferences in regard to the ligand structure and conformation.[1] Interestingly, fatty acids such as palmitic acid and oleic acid adopt a U-shaped conformation when bound to FABPs.[1,2] The U-shaped conformation of the fatty acids is stabilized by electrostatic and hydrogen-bonding interactions with polar residues of the FABPs, and by van der Waals contacts with hydrophobic and aromatic residues lining the binding pocket. Although alkyl chains are known to take unusual conformations, such as a helical conformation when bound to synthetic receptors,[3] there is no unequivocally proven example of a U-shaped conformation of an alkane bound to a synthetic host.[4] Herein we report, for the first time, a U-shaped conformation of alkyl chains bound to a cyclic synthetic host which has been unequivocally characterized by NMR spectroscopy, X-ray crystallography, and isothermal titration calorimetry (ITC).

Cucurbit[*n*]uril (CB[*n*], $n = 5$–10), a family of host molecules comprising *n* glycoluril units, have a hydrophobic cavity and two identical carbonyl-laced portals.[5] Athough the cavity sizes of CB[7] and CB[8] are comparable to those of β- and γ-cyclodextrins, respectively, they exhibit extraordinary host–guest properties[6,7] that are distinctly different from those of the cyclodextrins. Despite extensive studies on the host–guest chemistry of CB[*n*],[6] however, little attention has been paid to the interaction of CB[*n*] with amphiphilic molecules containing a long alkyl chain.[8] We thus decided to investigate the formation of a host–guest complex between CB[*n*] ($n = 7$ and 8) and the alkyltrimethylammonium ion ($(CH_3)_3N^+C_mH_{2m+1}$, C_mTA^+, $m = 8$, 10, 12).

Both CB[7] and CB[8] form 1:1 host–guest complexes (**1** and **2**, respectively) with $C_{12}TA^+$, but the dodecyl chain of the guest takes totally different conformations in the complexes (Scheme 1), as confirmed by various NMR methods. The ^1H NMR spectra of $C_{12}TA^+$ bound to CB[7] and CB[8] are shown in Figure 1. In the case of **1** (Figure 1b), the signals of



Scheme 1. 1:1 host–guest complexes (**1** and **2**) formed between $C_{12}TA^+$ and CB[7] and CB[8], respectively.

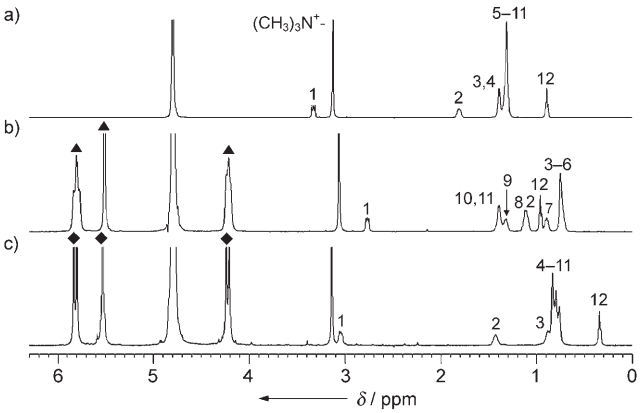


Figure 1. ^1H NMR spectra of $C_{12}TA^+$ in the a) absence of CB[*n*], and in the presence of 1 equivalent of b) CB[7] (▲) and c) CB[8] (◆) in D_2O at 25 °C.

the methylene protons close to the ammonium head group (C1–C7) are shifted to higher field by $\delta = 0.4$–0.7 ppm relative to those of the free $C_{12}TA^+$ ion (Figure 1a), whereas no significant change in the chemical shifts are observed for the terminal part (C8–C12) of the aliphatic chain. These findings indicate that CB[7] is located over the aliphatic part of $C_{12}TA^+$ close to the ammonium group, as illustrated in Scheme 1.

In **2**, however, all the protons of the long alkyl chain experience a considerable upfield shift, while those of the trimethylammonium group exhibit a small downfield shift (Figure 1c). The upfield shift of the aliphatic protons becomes more pronounced on moving from C1 to C12 (see Table S1 in the Supporting Information). The terminal methyl protons in particular show the largest upfield shift ($\Delta\delta = 0.54$ ppm), thus

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indicating that the methyl group is buried deeply inside the CB[8] cavity. This observation suggests that in **2** the long aliphatic chain of $C_{12}TA^+$ folds back in the cavity of CB[8] (Scheme 1). Furthermore, the much shorter spin-lattice relaxation times (T_1) of the aliphatic protons in **2** compared to those of **1** or free $C_{12}TA^+$ (see Table S2 in the Supporting Information) reflect a highly restricted motion of the long alkyl chain inside CB[8]. ROESY data for **2** (see Figure S3 in the Supporting Information) revealed intramolecular NOE cross-peaks between the terminal methyl protons and the trimethylammonium protons, which indicates that the terminal methyl group is very close to the ammonium group. The methylene protons of CB[8] interact, in an intermolecular fashion, with the trimethylammonium protons and several methylene protons at the middle of the aliphatic chain, which corresponds to the turning point of the folded chain. Taken together, the NMR data indicate that the long alkyl chain of the guest adopts a U-shaped conformation inside the CB[8] cavity while the positively charged ammonium group interacts with one of the carbonyl-fringed portals, as illustrated in Scheme 1. Surfactants with a shorter alkyl chain (C_mTA^+, $m =$ 8 and 10) also adopt a U-shaped conformation when bound to CB[8], as judged by NMR spectroscopic analysis (see the Supporting Information).

X-ray structure analysis provided unequivocal proof of the U-shaped conformation of the alkyl chains. After numerous unsuccessful attempts, single crystals of the complexes of CB[8] with C_mTA^+ ($m = 8, 10, 12$) suitable for X-ray analysis using synchrotron radiation were grown from an aqueous solution in a sealed tube under hydrothermal conditions. The X-ray crystal structures of the host–guest complexes (Figure 2) revealed that the aliphatic chains of the guests buried deeply inside the cavity adopt a U-shaped conformation as suggested by the NMR studies. The folded conformations of C_8, C_{10}, and C_{12} have anticlinal as well as *gauche* forms. The conformation of the octyl chain is *t-g-g-ac-t-ac* (*t* = *trans*, *g* = *gauche*, and *ac* = *anticlinal*) with torsion angles of 177, 157, 100, 81, 52, 146, 168, and 88°, respectively. The decyl and dodecyl chains have conformations close to *t-t-ac-g-g-ac-t-g* and *t-t-g-g-ac-g-g-g-t-g*, respectively. Consistent with the ROESY results, the terminal methyl group is located in proximity to the trimethylammonium group. The shortest distances between a methyl carbon atom of the trimethylammonium group and the terminal methyl carbon atoms of C_8, C_{10}, and C_{12} are 4.33, 3.73, and 3.65 Å, respectively. A significant ellipsoidal deformation of the host to accommodate the guests in a U-shaped conformation was observed, thereby providing a better shape complementarity (see Figure S6 in the Supporting Information). The ammonium group of the guests is located just outside of the portal, while leaning toward a narrow side of the portal to maximize its interaction with the carbonyl groups of the host.

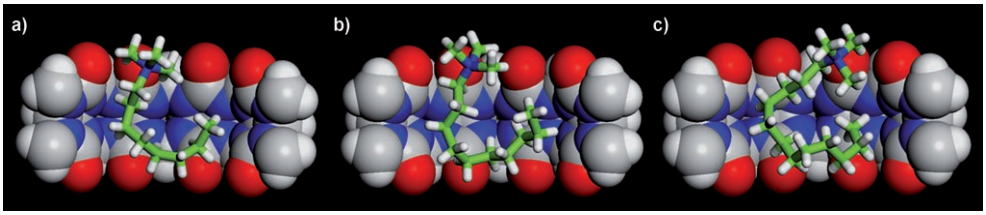

Figure 2. X-ray crystal structures of a) CB[8]·C_8TA^+, b) CB[8]·$C_{10}TA^+$, and c) CB[8]·$C_{12}TA^+$.

To understand the thermodynamics associated with the complexation of $C_{12}TA^+$ with CB[7] and CB[8] we carried out ITC experiments (Table 1). $C_{12}TA^+$ binds to CB[8] more tightly than to CB[7] by a factor of 5. The complexation of $C_{12}TA^+$ with CB[7] is driven by both enthalpy and entropy, while the formation of the CB[8]·$C_{12}TA^+$ complex is almost exclusively enthalpy driven. The complexation with CB[8] is enthalpically more favorable than that with CB[7] by about 17 kJ mol^{-1}, which is presumably due to the increased van der Waals contact between the folded aliphatic chain and the inner wall of the host cavity. The large positive entropy change for formation of the CB[7] complex results from extensive dehydration of the CB portals and cavity upon complexation.[9] The near-zero entropy change observed on formation of the CB[8] complex suggests that the entropic gain from dehydration cancels out the loss of entropy arising from the severe conformational restriction of the U-shaped guests bound in the host. On the basis of these results we conclude that, despite the high internal strain (35–60 kJ mol^{-1}),[10] the guests take the U-shaped conformation to maximize the van der Waals contact between the alkyl chain and the inner wall of the CB[8] cavity and to minimize the surface area of the hydrophobic alkyl chain exposed to water. It should be noted that a similarly high binding constant, large enthalpic gain, and near-zero entropy change have been observed for the binding of a saturated fatty acid (C_{12}) to FABP.[2c]

Table 1: Binding constants (K) and the relevant thermodynamic parameters for the complexation of $C_{12}TA^+$ with CB[7] and CB[8].[a]

Host	K [M^{-1}]	$H°$ [kJ mol^{-1}]	$T\Delta S°$ [kJ mol^{-1}]
CB[7]	$(5.8\pm0.1)\times10^5$	-21.9 ± 0.1	11.0 ± 0.1
CB[8]	$(2.8\pm0.1)\times10^6$	-38.7 ± 0.1	-1.9 ± 0.1

[a] In 50 mM NaO_2CCH_3 buffer solution at $T = 298$ K.

As suggested by the NMR spectroscopic, X-ray, and thermodynamic analysis, the U-shaped conformation of C_mTA^+ bound to CB[8] is stabilized by electrostatic interactions with the polar carbonyl groups at the portal of CB[8] and by van der Waals interactions with the hydrophobic cavity of CB[8], in a similar way that a U-shaped conformation of fatty acids bound to FABPS is stabilized. The hollowed-out pumpkin-shaped cavity of CB[8] also resembles the spherical binding sites of FABPs[1a] to which fatty acids are bound in a U-shaped conformation, although the cavity volume of the former[6b] is somewhat smaller than that of the latter. The

smaller and more-rigid cavity of CB[8] seems to make the bound alkyl chains more strained compared with those bound to FABPs.

In summary, we have discovered that alkyl chains adopt a U-shaped conformation in the cavity of CB[8], similar to that found for fatty acids bound to FABPs. To the best of our knowledge, this is the first example of a U-shaped conformation of alkyl chains bound to a synthetic receptor which has been unequivocally characterized by NMR spectroscopy, ITC, and X-ray crystallography. The unique structural features of CB[8]—the shallow but wide cavity with a diameter of 8.8 Å and narrow, partially negatively charged portals[5,6]—provide a perfect binding site for long alkylammonium ions in a U-shaped conformation. This result is in sharp contrast to the cavitands and capsules developed by Rebek and coworkers which have a narrow but deep cylindrical cavity with a diameter of 6.6 Å: in these systems the alkanes adopt a helical conformation to maximize the CH–π interactions with the aromatic surface of the hosts.[3] The discovery of the unusual back-folding of alkyl chains in a synthetic host not only sheds light on the binding of fatty acids to FABPs, but may also provide an insight into designing molecular machines and switches based on folding/unfolding motion.[11]

Experimental Section

Materials and methods: The alkyltrimethylammonium ($(CH_3)_3N^+C_mH_{2m+1}$, $m = 8$, 10, 12) bromides and solvents employed were used as supplied without further purification. The cucurbit[*n*]urils ($n = 7$, 8) were synthesized according to literature methods.[5a] All the NMR data were recorded on a Bruker DRX500 spectrometer operating at the proton Larmor frequency of 500.23 MHz. Isothermal titration calorimetry experiments were performed on a VP-ITC calorimeter from Microcal. Mass spectra were recorded on an ABI 4700 Proteomics Analyzer MALDI-TOF instrument.

CB[7]·$C_{12}TA^+$ (**1**): CB[7] (6.2 mg, 4.3 μmol) was added to a solution of C_{12}TABr (1.3 mg, 4.3 μmol) in D_2O (3 mL), and the resulting solution was sonicated until all the solid materials had dissolved. ^{1}H NMR (D_2O, 500 MHz, 25 °C): $\delta = 5.81$ (brs, 14H), 5.52 (s, 14H), 4.22 (brs, 14H), 3.06 (s, 9H), 2.77 (t, $J = 8.6$ Hz, 2H), 1.40 (brs, 4H), 1.32 (brs, 2H), 1.11 (brs, 4H), 0.96 (t, $J = 6.6$ Hz, 3H), 0.89 (brs, 2H), 0.75 ppm (brs, 8H); MS (MALDI-TOF): *m/z* (%): 1390.6 (100) $[M]^+$.

CB[8]·$C_{12}TA^+$ (**2**): CB[8] (7.6 mg, 4.3 μmol) was added to a solution of C_{12}TABr (1.3 mg, 4.3 μmol) in D_2O (3 mL), and the resulting solution was sonicated with occasional heating until all the solid material had dissolved. ^{1}H NMR (D_2O, 500 MHz, 25 °C): $\delta =$ 5.82 (d, $J = 15.1$ Hz, 16H), 5.53 (s, 16H), 4.23 (d, $J = 15.1$ Hz, 16H), 3.14 (s, 9H), 3.05 (t, $J = 8.0$ Hz, 2H), 1.43 (brs, 2H), 0.88 (brs, 2H), 0.83 (brsV, 8H), 0.80 (brs, 4H), 0.76 (brs, 4H), 0.34 ppm (t, $J =$ 8.0 Hz, 3H); MS (MALDI-TOF): *m/z* (%): 1556.6 (100) $[M]^+$.

Single-crystal X-ray crystallography: Diffraction data for CB[8]·C_mTA^+ ($m = 8$, 10, 12) were collected at 90 K on a ADSC Quantum 210 CCD diffractometer with synchrotron radiation. Structures were solved (direct methods) and refined (full-matrix least-squares on F^2) using the SHELXTL program package. Crystal data for CB[8]·C_8TABr: $C_{59}H_{106}N_{33}O_{32}Br$, $M_r = 1869.68$, monoclinic, space group $P2_1$, $a = 13.898(3)$, $b = 20.472(4)$, $c = 15.404(3)$ Å, $\beta =$ 104.79(3)°, $V = 4238(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.465$ g cm^{-3}, $R_1 = 0.1237$ ($I > 2\sigma(I)$), $wR_2 = 0.3750$ (all data), GOF = 1.813. Crystal data for CB[8]·C_{10}TABr: $C_{61}H_{110}N_{33}O_{32}Br$, $M_r = 1897.73$, monoclinic, space group $P2_1$, $a = 13.334(3)$, $b = 20.593(4)$, $c = 15.411(3)$ Å, $\beta =$ 103.84(3)°, $V = 4109(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.534$ g cm^{-3}, $R_1 = 0.0841$ ($I > 2\sigma(I)$), $wR_2 = 0.2549$ (all data), GOF = 1.062. Crystal data for CB[8]·C_{12}TABr: $C_{63}H_{107.5}N_{33}O_{28.75}Br$, $M_r = 1867.23$, monoclinic, space group $P2_1$, $a = 13.464(3)$, $b = 20.579(4)$, $c = 15.390(3)$ Å, $\beta =$ 104.00(3)°, $V = 4138(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.502$ g cm^{-3}, $R_1 = 0.0819$, ($I > 2\sigma(I)$), $wR_2 = 0.2326$ (all data), GOF = 1.050. CCDC 676779 (CB[8]·C_8TABr), 676780 (CB[8]·C_{10}TABr), and 676781 (CB[8]·C_{12}TABr) 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

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