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Mikhail V. Rekharsky[a]; Young Ho Ko[b]; N. Selvapalam[b]; Kimoon Kim[b]; Yoshihisa Inoue[a]
[a] Entropy Control Project, ICORP, JST, Toyonaka, Japan [b] Division of Molecular and Life Sciences, National Creative Research Initiative Center for Smart Supramolecules and Department of Chemistry, Pohang University of Science and Technology, Pohang, South Korea

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Complexation Thermodynamics of Cucurbit[6]uril with Aliphatic Alcohols, Amines, and Diamines

MIKHAIL V. REKHARSKY[a], YOUNG HO KO[b], N. SELVAPALAM[b], KIMOON KIM[b,*] and YOSHIHISA INOUE[a,*]

[a]*Entropy Control Project, ICORP, JST, 4-6-3 Kamishinden, Toyonaka 560-0085, Japan;* [b]*Division of Molecular and Life Sciences, National Creative Research Initiative Center for Smart Supramolecules and Department of Chemistry, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, South Korea*

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Using the isothermal calorimetric titration technique, we determined the stability constants (K), reaction enthalpy (ΔH°), and entropy (ΔS°) for complexation of cucurbit[6]uril (CB[6]) with a series of aliphatic alcohols, mono- and diamines, as well as spermidine and spermine, in aqueous solutions of alkali metal chlorides. The K for spermine reached $5.4 \times 10^{10}\,M^{-1}$ in 0.2 M LiCl, which is the largest amongst the values reported for CB[6]. Propylamine forms the strongest 1:1 complex with CB[6] ($K = 21000\,M^{-1}$) in 0.1 M Na acetate buffer, which is driven exclusively by entropy. A comparison of K for 1,3-propanediamine versus 1,4-butanediamine reveals an extraordinary >60000-fold enhancement in affinity, which is the largest increment/CH_2 ever observed in supramolecular chemistry. The present results in combination with our ESI-MS data reported recently unambiguously demonstrate that CB[6] exists in aqueous solution of alkali metal salts exclusively as a dicationic species, e.g. $[CB[6]{\cdot}2Na]^{2+}$.

Keywords: Complex stability; Cucurbit[6]uril; Calorimetry; Alkanol; Alkylamine; Alkanediamine

INTRODUCTION

In their pioneering work, Mock and Shih [1] examined a wide variety of aliphatic and aromatic amines as guests for cucurbit[6]uril (CB[6]; Fig. 1). Probably due to the extremely low solubilities in any conventional solvents, the complex stabilities (K) were determined in 50% (v/v) aqueous formic acid by using the NMR and/or UV methods. Since then, complexation behavior of CB[6] has been studied not only in highly acidic 50% formic acid but also in neutral aqueous solutions of various metal salts and even in pure water. Recently, Isaacs et al. [2] have carefully reviewed the complexation behavior of CB[6] and other CBs to find large differences in K determined by different groups. For example, Buschmann et al. [3] reported $K = 6.6 \times 10^5\,M^{-1}$ for complexation of tricationic spermidine with CB[6] in pure water, which is 20 times lower than that determined in 50% formic acid by Mock et al. [1]. Isaacs et al. [4] reported $K = 4.5 \times 10^8\,M^{-1}$ for complexation of 1,6-hexanediammonium with CB[6] in 50 mM acetate buffer in D_2O (pD 4.74), which is >150 times larger than that determined in 50% formic acid by Mock et al. [1]. Obviously, varying solvent is one of the major reasons for giving such different K values, and the lack of systematic studies is hampering the mutual comparison and deeper understanding of the host–guest interactions in CB complex. This apparently controversial and puzzling situation prompted us to undertake a systematic study on complexation thermodynamics of CB[6] in aqueous solutions.

EXPERIMENTAL

Microcalorimetric experiments were performed using isothermal titration calorimeter VP-ITC (MicroCal, USA). Each experiment consisted of 25–55 consecutive injections (5–10 μL) of solution of aliphatic alcohol, mono- or diamine into microcalorimetric reaction cell (1.4 mL) charged with the solution of cucurbit[6]uril. Heat of reaction was corrected for the heat of dilution of aliphatic alcohol, mono- or diamine solution determined in separate experiments. All solutions were degassed prior titration experiment according to procedures pro-

*Corresponding author. E-mail: inoue@chem.eng.osaka-u.ac.jp

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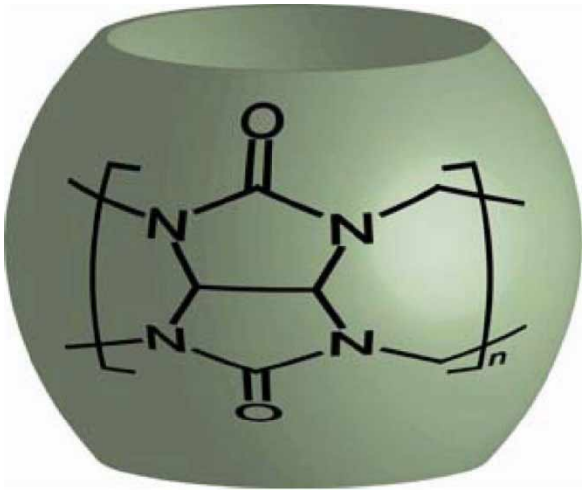

FIGURE 1 Chemical structure of cucurbit[6]uril (n = 6).

vided by MicroCal, Inc. Computer simulations (curve fitting) were performed using ORIGIN 7.0 software adapted for ITC data analysis. In cases of 1:1 complex formation Single Set of Identical Sites model was applied however in the cases of 1:2 complex formation experimental data were treated using Sequential Binding Sites model.

RESULTS AND DISCUSSION

CB[6] Species Existing in Aqueous Solution

To start any complexation thermodynamic study, one should know the molecular/ionic species existing in the solution. Surprisingly, there is no agreement in the literature on the identity of ionic form(s) of CB[6] solubilized in aqueous solution of metal salts. Buschmann et al. [5–7] reported that aqueous NaCl solution of CB[6] contains predominantly monocationic $[CB[6]\cdot Na]^+$ species. However, our recent ESI-MS study [8] has revealed that only dicationic $[CB6\cdot 2Na]^{2+}$ species exists even in the presence of a large excess of CB[6]. In this paper, we wish to present and discuss the systematic and comprehensive thermodynamic data for complexation of aliphatic amines and alcohols with CB[6] in a variety of aqueous solutions and also to reinforce our previous conclusion obtained by the ESI-MS study [8].

We first performed the microcalorimetric titration of CB[6] with propylammonium in aqueous 0.2 M LiCl, 0.05 M NaCl, and 0.05 M CsCl solutions (the higher LiCl concentration was needed due to the low solubility of CB[6] in aqueous LiCl solution). Propylammonium as guest has two advantages in the present case. Firstly, it shows a relatively high affinity toward CB[6] [1], and hence we can determine the stability constant with high precision. Secondly, judging from the geometrical dimensions, the short alkyl chain of propylammonium can be comfortably accommodated in the CB[6] cavity without touching the metal ion at the CB's second portal. Upon complexation with CB[6], the ammonium moiety of the guest coordinates to the carbonyl oxygens at one of CB[6] portals, while the hydrophobic part occupies the inner space of CB[6] [1,2]. If CB[6] exists in a monocationic form ($[CB[6]\cdot M]^+$; M = Li, Na, or Cs) and only one portal is occupied by metal ion, alkylammonium guest can readily penetrate into the cavity from the open end of CB without competing with the metal ion at the opposite portal. In the propylammonium case, the insertion of short propyl chain does not significantly affect the original position/location of the metal ion at the opposite end. Consequently, the stability constants as well as the other thermodynamic parameters would resemble to each other in all three solutions of 0.2 M LiCl, 0.05 M NaCl, and 0.05 M CsCl. In contrast, both the affinity and the enthalpic gain gradually decrease with increasing size of the metal ion, i.e. on going from 0.2 M LiCl to 0.05 M NaCl and than to 0.05 M CsCl, as shown in Table I. This thermodynamic behavior is compatible only with the dicationic form of CB[6] in the initial state, where the both ends are occupied by M^+. Indeed, Cs^+ with a size matched to CB[6] portal leads to the strongest ion–dipole interactions, making Cs^+ the hardest competitor for in-coming propylammonium to give the lowest affinity and enthalpic gain in CsCl solution. On the other hand, Li^+ is the weakest competitor and therefore the highest affinity and enthalpic gain were obtained in LiCl solution. Figure 2a and b illustrate the coordination of Na^+ and Cs^+ ions to CB[6] portals.

The fact that diammonium guests exhibit much higher affinities than the corresponding monoammonium guests [1,2] is also taken as evidence for the existence of a dicationic host species $[CB[6]\cdot 2Na]^{2+}$ in the solution. Thus, the relative stability constants, K_{di}/K_{mono}, are much higher than unity and rapidly increase with increasing alkyl chain length at least up to C7; i.e., $K_{di}/K_{mono} = 6.5$, 68, 1740, 2930, and 514 for C_4–C_8 guests (Table I). The steady increase of K_{di}/K_{mono} up to C_7 is readily explained by the coordination of sodium ions at both portals. In the alkylammonium cases, the affinity rapidly saturates at C_4—C_5 and decreases thereafter, as a result of the unfavorable displacement of capping Na^+ by the alkyl tail (Fig. 2c). In sharp contrast, complexation of α,ω-alkanediammonium by CB[6] is associated with the replacement of two Na^+ ions at both portals, and the flexible methylene backbone, unless too long, facilitates the optimized coordination of two ammonium groups at both portals. The thermodynamic advantage for alkanediammonium is obvious. The alkyl tail of monoammonium guest simply destabilizes the Na^+ remaining at the opposite

TABLE I Complex stability constant (K), standard free energy ($\Delta G°$), enthalpy, and entropy changes ($T\Delta S°$) for complexation of various guests toward cucurbit[6]uril (CB[6]) in aqueous solutions at $T = 298.15$ K

Reaction	K/M^{-1}	$\Delta G°/kJ\,mol^{-1}$	$\Delta H°/kJ\,mol^{-1}$	$T\Delta S°/kJ\,mol^{-1}$
$[CB6{\cdot}2Na]^{2+}$ + Ethanol = $[CB6{\cdot}Ethanol{\cdot}2Na]^{2+}$ (0.05 M NaCl)	90 ± 8	−11.2 ± 0.3	−11.2 ± 0.2	0.0 ± 0.4
$[CB6{\cdot}2Cs]^{2+}$ + Ethanol = $[CB6{\cdot}Ethanol{\cdot}2Cs]^{2+}$ (0.05 M CsCl)	26 ± 5	−8.1 ± 0.5	−9.1 ± 0.3	−1.0 ± 0.6
$[CB6{\cdot}2Na]^{2+}$ + Propanol = $[CB6{\cdot}Propanol{\cdot}2Na]^{2+}$ (0.05 M NaCl)	710 ± 30	−16.3 ± 0.1	−22.5 ± 0.2	−6.2 ± 0.2
$[CB6{\cdot}2K]^{2+}$ + Propanol = $[CB6{\cdot}Propanol{\cdot}2K]^{2+}$ (0.05 M KCl)	490 ± 20	−15.4 ± 0.2	−19.9 ± 0.2	−4.5 ± 0.3
$[CB6{\cdot}2Rb]^{2+}$ + Propanol = $[CB6{\cdot}Propanol{\cdot}2Rb]^{2+}$ (0.05 M RbCl)	120 ± 15	−11.9 ± 0.4	−16.8 ± 0.2	−4.9 ± 0.5
$[CB6{\cdot}2Cs]^{2+}$ + Propanol = $[CB6{\cdot}Propanol{\cdot}2Cs]^{2+}$ (0.05 M CsCl)	< 5			
$[CB6{\cdot}2Na]^{2+}$ + Butanol = $[CB6{\cdot}Butanol{\cdot}2Na]^{2+}$ (0.05 M NaCl)	1220 ± 50	−17.6 ± 0.1	−30.3 ± 0.3	−12.7 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + Pentanol = $[CB6{\cdot}Pentanol{\cdot}2Na]^{2+}$ (0.05 M NaCl)	410 ± 20	−14.9 ± 0.1	−24.1 ± 0.3	−9.2 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + Ethylammonium^{+} = $[CB6{\cdot}Ethylammonium{\cdot}Na]^{2+}$ + Na + (0.05 M NaCl)	990 ± 30	−17.1 ± 0.1	−9.3 ± 0.2	7.8 ± 0.2
$[CB6{\cdot}2Na]^{2+}$ + Ethylammonium^{+} = $[CB6{\cdot}Ethylammonium{\cdot}Na]^{2+}$ + Na + (0.1 M Na acetate buff.; pH 4.7)	130 ± 15	−12.1 ± 0.4	13.5 ± 0.4	25.6 ± 0.6
$[CB6{\cdot}2Na]^{2+}$ + 1-Propylammonium^{+} = $[CB6{\cdot}1\text{-}Propylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M NaCl)	$(1.55 \pm 0.08) \times 10^5$	−29.7 ± 0.1	−19.1 ± 0.3	10.6 ± 0.3
$[CB6{\cdot}2Cs]^{2+}$ + 1-Propylammonium^{+} = $[CB6{\cdot}1\text{-}Propylammonium{\cdot}Cs]^{2+}$ + Cs^{+}(0.05 M CsCl)	8500 ± 500	−22.4 ± 0.2	−9.2 ± 0.4	13.2 ± 0.5
$[CB6{\cdot}2Li]^{2+}$ + 1-Propylammonium^{+} = $[CB6{\cdot}1\text{-}Propylammonium{\cdot}Li]^{2+}$ + Li^{+}(0.2 M LiCl)	$(2.2 \pm 0.1) \times 10^6$	−36.2 ± 0.1	−41.7 ± 0.4	−5.5 ± 0.4
$[CB6{\cdot}2Na]^{2+}$ + 1-Propylammonium^{+} = $[CB6{\cdot}1\text{-}Propylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.1 M Na acetate buff.; pH 4.7)	$(2.1 \pm 0.7) \times 10^4$	−24.7 ± 1.0	4.0 ± 0.5	28.7 ± 1.0
$[CB6{\cdot}2Na]^{2+}$ + 1-Propylammonium^{+} = $[CB6{\cdot}1\text{-}Propylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M Na citrate buff.; pH 4.5)	$(1.56 \pm 0.09) \times 10^5$	−29.6 ± 0.1	−18.9 ± 0.3	10.7 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + 1-Propylammonium^{+} = $[CB6{\cdot}1\text{-}Propylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M Na citrate buff.; pH 3.1)	$(1.55 \pm 0.09) \times 10^5$	−29.6 ± 0.1	−19.3 ± 0.3	10.3 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + Acetic acid^{0} = $[CB6{\cdot}Acetic\ acid{\cdot}2Na]^{2+}$ (0.05 M Na citrate buff.; pH 3.1)	150 ± 5	−12.4 ± 0.1	−24.0 ± 0.3	−11.6 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + 1-Butylammonium^{+} = $[CB6{\cdot}1\text{-}Butylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M NaCl)	$(3.1 \pm 0.2) \times 10^6$	−37.1 ± 0.1	−28.7 ± 0.3	8.4 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + 1-Pentylammonium^{+} = $[CB6{\cdot}1\text{-}Pentylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M NaCl)	$(2.2 \pm 0.1) \times 10^6$	−36.2 ± 0.1	−30.5 ± 0.4	5.7 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + 1-Hexylammonium^{+} = $[CB6{\cdot}1\text{-}Hexylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M NaCl)	$(1.67 \pm 0.08) \times 10^5$	−29.8 ± 0.1	−25.1 ± 0.3	4.7 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + 1-Heptylammonium^{+} = $[CB6{\cdot}1\text{-}Heptylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M NaCl)	5800 ± 150	−21.5 ± 0.1	−18.9 ± 0.3	2.6 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + 1-Octylammonium^{+} = $[CB6{\cdot}1\text{-}Octylammonium{\cdot}Na]^{2+}$ + Na^{+}(0.05 M NaCl)	2100 ± 100	−19.0 ± 0.2	−16.9 ± 0.3	2.1 ± 0.3
$[CB6{\cdot}2Na]^{2+}$ + Ethylenediammonium^{2+} = $[CB6{\cdot}Ethylenediammonium{\cdot}Na]^{3+}$ + Na^{+}(0.05 M NaCl)	200 ± 50	−13.1 ± 0.7	0.9 ± 0.3	14.0 ± 0.8
$[CB6{\cdot}Ethylenediammonium{\cdot}Na]^{3+}$ + Ethylenediammonium^{2+} = $[CB6{\cdot}2Ethylenediammonium]^{4+}$ + Na^{+}(0.05 M NaCl)	≈15		≈ −8	
$[CB6{\cdot}2Na]^{2+}$ + 1,3-Propanediammonium^{2+} = $[CB6{\cdot}1,3\text{-}Propanediammonium{\cdot}Na]^{3+}$ + Na^{+}(0.05 M NaCl)	330 ± 50	−14.4 ± 0.4	1.5 ± 0.3	15.9 ± 0.5
$[CB6{\cdot}1,3\text{-}Propanediammonium{\cdot}Na]^{3+}$ + 1,3-Propanediammonium^{2+} = $[CB6{\cdot}2(1,3\text{-}Propanediammonium)]^{4+}$ + Na^{+}(0.05 M NaCl)	≈7		≈ −9	
$[CB6{\cdot}2Na]^{2+}$ + 1,4-Butanediammonium^{2+} = $[CB6{\cdot}1,4\text{-}Butanediammonium]^{2+}$ + $2Na^{+}$(0.05 M NaCl)	$(2.0 \pm 0.2) \times 10^7$	−41.6 ± 0.3	−28.2 ± 0.3	13.4 ± 0.4
$[CB6{\cdot}2Na]^{2+}$ + Spermidine^{3+} = $[CB6{\cdot}Spermidine]^{3+}$ + $2Na^{+}$(0.05 M NaCl)	$(4.1 \pm 0.3) \times 10^8$	−49.2 ± 0.2	−35.0 ± 0.4	14.2 ± 0.5
$[CB6{\cdot}2Na]^{2+}$ + Spermine^{4+} = $[CB6{\cdot}Spermine]^{4+}$ + $2Na^{+}$(0.05 M NaCl)	$(3.3 \pm 0.4) \times 10^9$	−54.3 ± 0.2	−38.8 ± 0.4	15.5 ± 0.5
$[CB6{\cdot}2Li]^{2+}$ + Spermine^{4+} = $[CB6{\cdot}Spermine]^{4+}$ + $2Li^{+}$(0.2 M LiCl)	$(5.4 \pm 0.5) \times 10^{10}$	−61.3 ± 0.2	−67.7 ± 0.7	−6.4 ± 0.7
$[CB6{\cdot}2Na]^{2+}$ + 1,5-Pentanediammonium^{2+} = $[CB6{\cdot}1,5\text{-}Pentanediammonium]^{2+}$ + $2Na^{+}$(0.05 M NaCl)	$(1.5 \pm 0.1) \times 10^8$	−46.7 ± 0.2	−30.3 ± 0.4	16.4 ± 0.5
$[CB6{\cdot}2Na]^{2+}$ + 1,6-Hexanediammonium^{2+} = $[CB6{\cdot}1,6\text{-}Hexanediammonium]^{2+}$ + $2Na^{+}$(0.05 M NaCl)	$(2.9 \pm 0.2) \times 10^8$	−48.3 ± 0.2	−34.7 ± 0.4	13.6 ± 0.5
$[CB6{\cdot}2Na]^{2+}$ + 1,7-Heptanediammonium^{2+} = $[CB6{\cdot}1,7\text{-}Heptanediammonium]^{2+}$ + $2Na^{+}$(0.05 M NaCl)	$(1.7 \pm 0.2) \times 10^7$	−41.2 ± 0.3	−30.4 ± 0.3	10.8 ± 0.4
$[CB6{\cdot}2Na]^{2+}$ + 1,8-Octanediammonium^{2+} = $[CB6{\cdot}1,8\text{-}Octanediammonium]^{2+}$ + $2Na^{+}$(0.05 M NaCl)	$(1.08 \pm 0.06) \times 10^6$	−34.4 ± 0.3	−25.5 ± 0.3	8.9 ± 0.4
$[CB6{\cdot}2Na]^{2+}$ + 1,10-Decanediammonium^{2+} = $[CB6{\cdot}1,10\text{-}Decanediammonium]^{2+}$ + $2Na^{+}$(0.05 M NaCl)	$(1.67 \pm 0.06) \times 10^4$	−24.1 ± 0.2	−18.8 ± 0.3	5.3 ± 0.3

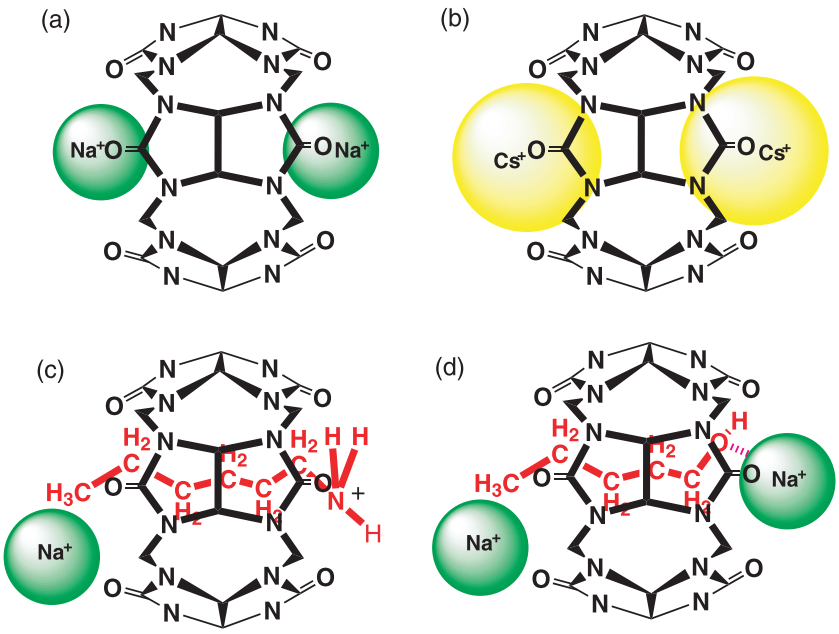

FIGURE 2 Coordination of (a) sodium and (b) cesium ions to the portals of CB[6] and dislocation of the sodium ion upon inclusion of (c) hexylammonium and (d) pentanol in the cavity.

end of CB, whilst the second ammonium group of alkanediammonium guest rather accelerates the complexation through coordination to the second portal as far as the methylene chain is accommodated in the cavity. Now, it is clear that the difference in saturating behavior of K for mono- and diamine leads to the increasing trend of the K_{di}/K_{mono} value and this advantage of diamine never vanish even after the value reaches the maximum at C_7.

We also examined a series of C_2—C_5 alkanols as guests for CB[6] in aqueous 0.05 M NaCl solution. Complexation of neutral guests, such as aliphatic alcohols, ketones, and ethers, with CB[6] is facilitated by coordination of guest's oxygen to the metal ion at one of CB[6] portals as well as the insertion of hydrophobic moiety into the cavity [9–11]. If CB[6] exists in monocationic form (e.g. $[CB[6]{\cdot}Na]^+$) and the second portal is open, we may expect a continuously increasing trend in K with increasing alkyl chain length, as was the case with cyclodextrins [12]. On the other hand, if both portals are capped with sodium ions, the maximum affinity should be observed for an alcohol with the optimum alkyl chain length that can be comfortably accommodated in the cavity. Further extension of the alkyl chain should cause steric clashes with the sodium ion (Fig. 2d), leading to a reduced affinity. The results in Table I support the coordination of sodium ions to both portals. Indeed, the affinity becomes higher on going from ethanol to propanol and then to butanol, but is suddenly reduced upon further elongation of the alkyl chain.

We further investigated the complexation of propanol in aqueous NaCl, KCl, RbCl, and CsCl solutions (0.05 M). By manipulating the cation size, we wanted to control the effective accessible volume of CB[6] cavity (Fig. 2a and 2b). If both portals are occupied by metal ions, the inner volume of CB[6] cavity is gradually reduced by increasing the cation size from Na^+ to Cs^+ with accompanying decrease in K. Indeed, the ITC results show that the affinity of propanol decreases from 710 M^{-1} in NaCl solution to 490 M^{-1} in KCl solution and then to 120 M^{-1} in RbCl solution. In CsCl solution, we could not detect any appreciable complexation of propanol with CB[6]. Before giving a final conclusion, we should examine another interpretation of the observed tendency, in which the affinity decrease is related to the reduced coordination ability of cation to oxygen: $Na^+ > K^+ > Rb^+ > Cs^+$. This explanation seems reasonable, since the most strongly coordinating Na^+ affords the largest affinity to alcohol, whilst the weakly coordinating Cs^+ fails to bind the alcohol guest. To check this possibility we employed ethanol as a guest for CB[6] in 0.05 M CsCl solution to obtain an appreciable affinity of 26 M^{-1}, which is 3.5 times lower than that in 0.05 M NaCl solution (Table I). Consequently, if CB[6] exists as a monocationic species in aqueous solution, we should observe a similar trend in affinity by changing the salt from NaCl to CsCl even in the case of propanol and hence can expect K of ca. 200 M^{-1} in CsCl solution, which however obviously contradicts with the experimental data shown in Table I.

In conclusion, all the thermodynamic data reinforce our previous conclusion [8] that CB[6] is solubilized in aqueous solution of various metal salts by forming exclusively dicationic species.

Affinity of Alkylammonium Versus α, ω-Alkanediammonium Toward CB[6] in 50% Formic Acid and in 0.05 M NaCl Solution

Addition of formic acid (as high as 50%) into water leads to total restructuring of the unique structure of water, and hence it is difficult in general to expect similar complexation thermodynamic behavior in water and 1:1 water-formic acid mixture. Nevertheless, the profiles of affinity ($\log K$) for both alkylammonium and alkanediammonium guests toward CB[6] (as a function of chain length) are similar in these two solvents, as illustrated in Fig. 3. In both solvents, the affinity of C_2—C_8 alkylammonium guests gradually increases to reach a maximum at C_4 and then starts to decrease moderately to C_5 and rapidly thereafter. Similar affinity profiles are also seen for alkanediammonium guests with maxima at C_5—C_6.

The reaction enthalpies determined (Table I) exhibit a trend very similar to that observed for affinity (see above). The reaction enthalpy reaches the largest negative value at C_4—C_5 for alkylammonium and at C_6 for alkanediammonium (Fig. 4a). The reaction entropy is consistently positive with a profile somewhat similar to that for affinity (Fig. 4b). Thus, the complexation of amines and diamines with CB[6] is driven and controlled by both enthalpic and entropic terms.

Interestingly, despite the continuous increase in enthalpy up to C_5, the reaction entropy starts to decrease at C_4 upon complexation of alkylammonium (Fig. 4), probably indicating appreciable conformational restriction of the alkyl chain in the cavity due to the steric clashes with Na^+ at the opposite portal. However, this entropic loss is overcompensated by the large per-methylene enthalpic gain of 9.6 kJ mol^{-1} most likely arising from the strong van der Waals interactions inside the cavity to give the largest affinity of 3.1×10^6 M^{-1} for butyammonium. Conformational restrictions are more severe for pentylammonium and the small enthalpic gain (1.8 kJ mol^{-1}) obtained by adding an extra methylene to butylammonium is completely cancelled out by a larger entropic loss (2.7 kJ mol^{-1}), eventually leading to a measurable reduction of affinity for pentylammonium. Volumes of longer alkylammonium guests exceed the available space of CB[6] cavity capped with a sodium ion. The only way to accommodate such a bulky guest is to displace the sodium ion from its optimal position/location at the opposite CB[6] portal (Fig. 2c). Obviously, such displacement is enthalpically highly unfavorable and leads to a large decrease in affinity.

In contrast, alkanediammonium guests can replace two sodium ions at both portals of CB[6]. However, the alkyl chains of 1,2-ethylenediammonium and 1,3-propanediammonium guests are too short to allow simultaneous coordination of the two ammonium groups to the both portal of CB[6]. This is the major reason why we observe particularly low affinities for

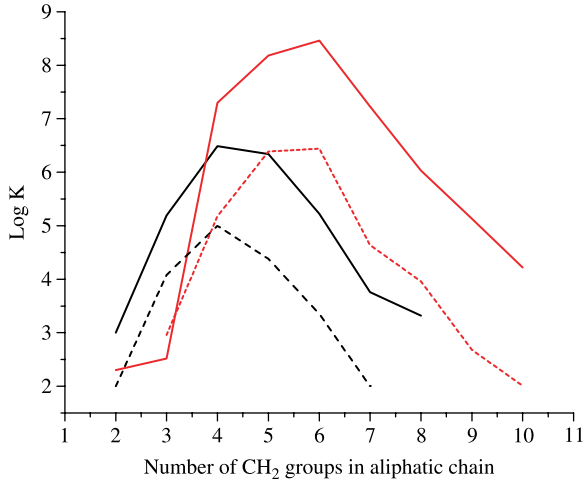

FIGURE 3 Affinity ($\log K$) of CB[6] toward monocationic alkylammonium guests in 0.05 M NaCl (black) and in 50% formic acid (black-dashed) and toward dicationic 1,ω-alkanediammonium guests in 0.05 M NaCl (red) and in 50% formic acid (red-dashed).

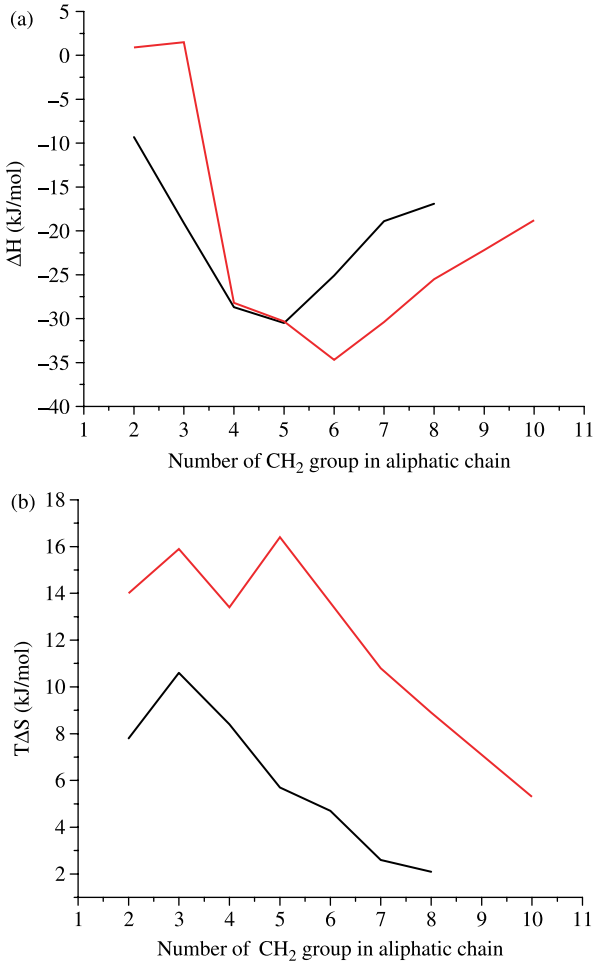

FIGURE 4 (a) Reaction enthalpy ($\Delta H°$) and (b) entropy ($T\Delta S°$; $T = 298.15$ K) for complexation of alkylammonium (black) and alkanediammonium (red) with CB[6].

these short C2 and C3 diamines (Table I). The dramatic affinity jump between C3 and C4 alkanediammonium guests leads us to a conclusion that at least four methylene units are needed for alkanediammonium guest to allow the simultaneous replacement of the two sodium ions at the both ends of CB[6]. The affinity is enhanced by 60000 times by simply adding a single methylene to propanediammonium. To the best of our knowledge, this is the largest per-methylene enhancement ever observed in supramolecular chemistry.

The more moderate affinity enhancement observed upon further extension of the alkyl chain from C_4 to C_5 is caused by more favorable enthalpy and entropy changes, which are attributable to the optimized van der Waals interactions (enthalpic gain) and the extensive cavity desolvation (entropic gain). The additional relatively small enhancement of affinity observed for hexanediammonium is exclusively enthalpy driven, probably due to very strong intra-cavity van der Waals interactions. However, as demonstrated in cyclodextrin complexation [13], strong intra-cavity van der Waals interactions inevitably lead to restriction of guest conformation with accompanying decrease of entropy (Table I). Then, the inherent entropic gain from the dehydration of host cavity is constantly cancelled upon extension of the methylene chain from C_6 to C_{10} (Table I). The enthalpic gain reaches the highest value at C_6 and then monotonically decreases up to C_{10}. Such a synchronized reduction of enthalpy and entropy is expected to occur when the alkyl chain length exceeds a certain limit. Thus, a very long alkyl chain is severely restricted in conformation inside the cavity (causing entropic losses) and at the same time two ammonium groups are poorly coordinated at the portals resulting in weak host–guest ion–dipole interactions (enthalpic losses).

Now, we interpret the complexation thermodynamic behavior in 50% formic acid. In a highly acidic solution of 50% formic acid, it is likely that concentration of hydronium ion (H_3O^+) is high enough to achieve effective coordination to CB[6] portals, forming $[CB[6]\cdot 2H_3O]^{2+}$ complex. This dicationic complex should behave in a way similar to $[CB[6]\cdot 2Na]^{2+}$ and therefore the general affinity profiles would resemble to each other for the same guest series. However, there is a problem with such explanation. As we discussed above, the affinity of propylammonium increases with decreasing cation size of metal salt in solution, and therefore we would expect higher affinity for $[CB[6]\cdot 2H_3O]^{2+}$ than for $[CB[6]\cdot 2Na]^{2+}$. To explain the experimentally observed lower affinity in 50% formic acid versus 0.05 M NaCl solution we should take into account the species residing in the CB[6] cavity. In 0.05 M NaCl solution, the cavity can contain several water molecules since there is no other possible guest species in NaCl solution. However, it is likely that in 50% formic acid, neutral HCOOH molecules are included in the cavity. These HCOOH molecules may act as competitor to reduce the affinity for alkylammoium and alkyldiammonium guests.

To explore the possible inclusion of organic acid into CB[6] cavity, we performed the ITC experiments with propylammonium in 3 different buffer solutions: 0.05 M Na citrate buffer at pH 4.5, 0.05 M Na citrate buffer at pH 3.1, and 0.1 M Na acetate buffer at pH 4.7. The thermodynamic parameters for complexation of propylammonium with CB[6] in 0.05 M Na citrate buffer (pH 4.5) and in 0.05 M Na citrate buffer (pH 3.1) are the same as those obtained in 0.05 M NaCl solution (Table I). This seems reasonable since bulky citric acid cannot be included in CB[6] cavity in any of these two solutions (Fig. 5a). In contrast, the use of 0.1 M Na acetate buffer greatly affected the complexation of propylammonium to give a 7.4-times smaller affinity and a positive enthalpy change (Table I). The most likely reason for the affinity drop in 0.1 M Na acetate buffer is the inclusion of neutral acetic acid (CH_3COOH, existing in the solution as a part acetic buffer) into the cavity (Fig. 5b). We performed ITC experiments and directly determined the thermodynamic parameters for complexation of neutral CH3COOH with CB[6] in 0.05 M Na citrate buffer (pH 3.1). This association is exclusively enthalpy-driven and accompanied by a large negative entropy (Table I and Fig. 5b). The complexation enthalpy of CH_3COOH with CB[6] is more negative than that of propylammonium (Table I). It is readily understood why the complexation of propylammonium with CB[6] is associated with an unfavorable positive enthalpy in 0.1 M Na acetate buffer. This is simply because the removal of neutral CH_3COOH from the cavity is not entirely compensated in enthalpy by the inclusion of propylammonium. This scenario is illustrated in Fig. 5c. In the ethylammonium case, even a larger positive enthalpy was obtained in 0.1 M Na acetate buffer. Again, the enthalpy difference in 0.05 M NaCl versus 0.1 M Na acetate buffer is close to the enthalpy of insertion of neutral CH_3COOH into the cavity.

By using the ITC results obtained in 0.05 M NaCl solution and in 0.1 M Na acetate buffer, we may explain similar affinities determine for 1,6-hexanediammonium in this study performed in 0.05 M NaCl solution and in Isaacs' study [4] performed in 0.05 M CD_3CO_2Na-buffered D_2O (pD 4.74) solution. These two studies were performed in different solvents, i.e. H_2O versus D_2O, but we assume that the solvent isotope effect does not lead to >15–20% difference in affinity, as was the case with cyclodextrin complexation [13]. As discussed above, the presence of neutral acetic acid molecules in 0.025 M CD_3CO_2Na-buffered D_2O (pD 4.74) should reduce the stability of 1,6-hexanediammonium-CB[6]

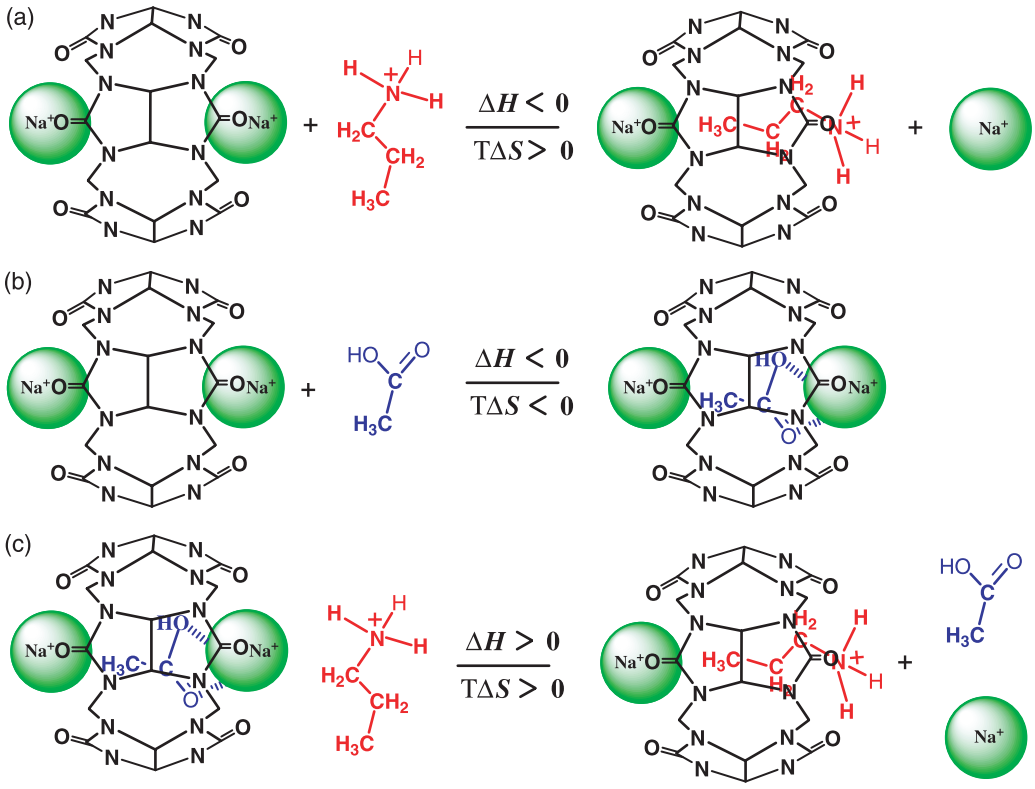

FIGURE 5 (a) Insertion of propylammonium into CB[6] cavity in 0.05 M NaCl, 0.05 M Na citrate buffer (pH 4.5), and 0.05 M Na citrate buffer (pH 3.1), where CB[6] cavity is occupied only by water molecule(s) (not shown); (b) Inclusion of neutral CH_3COOH molecule in CB[6] cavity; (c) Complexation of propylammonium with CB[6] in 0.1 M Na acetate buffer (pH 4.7).

complex. Taking into account the affinity of neutral acetic acid toward CB[6] (Table I), we may expect that the stability of 1,6-hexanediammonium-CB[6] complex in 0.025 M CD_3CO_2Na-buffered D_2O is 3–4 times lower than that in neutral solution that contains the same concentration of sodium ions, e.g. 0.025 M NaCl. This concentration is two times lower than that of our study (0.05 M NaCl). A low concentration of Na^+ means weaker competition for the CB[6] portals and thus stronger inclusion of 1,6-hexanediammonium. These two opposite trends, i.e. the presence of neutral acetic acid molecules in the solution (leading to an affinity reduction) versus the lower Na^+ concentration (leading to an affinity enhancement), counterbalance to each other to eventually afford the very similar complex stabilities in both solutions.

The geometric dimensions of CB[6] cavity allow inclusion of up to two molecules of neutral formic acid probably forming a hydrogen-bonded dimer in the cavity. This idea is supported by comparing the affinities of alkylammonium and alkanediammonium guests toward CB[6] in 0.05 M NaCl and in 50% formic acid. If there are two molecules of neutral formic acid in the cavity, then short alkylammonium guest, such as ethyl- or propylammonium, would replace only one of the two formic acids, while longer alkylammonium and alkanediammonium could replace both of the formic acid molecules. If this is the case, the difference in affinity (obtained in 0.05 M NaCl solution versus 50% formic acid) should be smaller for short alkylammonium than for longer alkylammonium and alkanediammonium. Indeed, the affinity ratio, K_{NaCl}/K_{HCOOH}, is close to 10 for ethyl- and propylammonium, but well exceeds 100 for longer alkylammonium and alkanediammonium guests. We may conclude therefore that the earlier data obtained in 50% formic acid [1] are well compatible with the present ITC data obtained in aqueous metal salt solutions.

Interaction of Spermidine and Spermine

As illustrated in Fig. 6 (color lines), diamines consistently display much higher affinities toward CB[6] than the corresponding monoamines. This general tendency prompted us to further examine the complexation thermodynamic behavior of biologically important polyamines, such as spermidine and spermine. These tri- and tetraammonium guests allow us to systematically investigate the effects of the number of ammonium groups in a guest. The affinities obtained for spermidine (3+) and spermine (4+) (Table I) are plotted against the number of ammonium groups in Fig. 6 (black line), along with the data for butylammonium (+) and butanediammonium (2+). Interestingly, the four points almost fall on a single straight line and each amino group

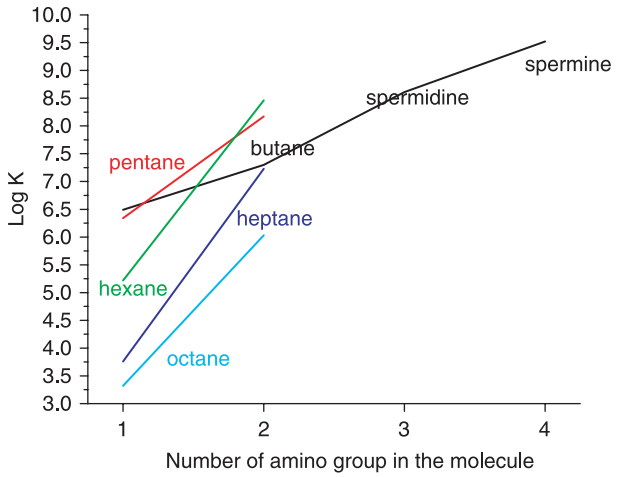

FIGURE 6 Dependence of complex stability upon the number of ammonium groups in guest molecule: i.e., alkanemonoamine (n = 1), alkanediamine (n = 2), spermidine (n = 3) and spermine (n = 4).

enhances the affinity by ca. 10 times ($\Delta \log K \approx 1$). The affinities for spermidine and spermine in 0.05 M NaCl (this study) are 306 and 250 times higher than those in 50% formic acid [1]. Such K_{NaCl}/K_{HCOOH} ratios are compatible with the above discussion.

However, it is very difficult to rationalize the absolute and relative affinities of 661,000 M^{-1} and 407,000 M^{-1} reported for complexation of CB[6] with spermidine and spermine in pure water [3], which are much smaller than those obtained in 0.05 M NaCl solution and even comparable to those reported in 50% formic acid and show an inverted selectivity for tricationic spermidine and tetracationic spermine [1]. Probably, the origin of such discrepancy arose from the use of an aqueous solution saturated with CB[6]. An ordinary sample of CB[6] always contains a small amount of other CBs, such as CB[7] and inverted CB[6]* [9–11;14], which are more soluble in pure water than CB[6]. Then, upon saturation of water by excess "CB[6]," the impurities are predominantly concentrated in the aqueous solution. If this most likely possibility is indeed the case, all the data obtained in pure water should be carefully reexamined [5–7].

Spermine shows the highest affinity of $3.3 \times 10^9\ M^{-1}$ in 0.05 M NaCl among the cationic and neutral guests examined in this study (Table I). In order to further enhance the stability of spermine-CB[6] complex, we performed the ITC measurements in 0.2 M LiCl solution, which reveals a 14-fold enhancement of affinity for propyammonium (Table I). As expected, the stability of spermine-CB[6] complex was also enhanced by 16 times in 0.2 M LiCl solution. Interestingly, the affinity enhancement is exclusively enthalpy-driven in both spermine and propylammonium cases and associated with large negative entropies. The increment of enthalpic gain ($\Delta\Delta H = \Delta H_{LiCl} - \Delta H_{NaCl}$) is substantially larger for spermine ($\Delta\Delta H = -28.9\ kJ\ mol^{-1}$) than for propylammonium ($\Delta\Delta H = -22.6\ kJ\ mol^{-1}$), simply because of a greater number of metal ions to be replaced upon complexation of spermine versus propylammonium. Similarly, the increment of entropic loss ($\Delta T\Delta S = T\Delta S_{LiCl} - T\Delta S_{NaCl}$) is larger for spermine ($\Delta T\Delta S = -21.9\ kJ\ mol^{-1}$) than for propylammonium ($\Delta T\Delta S = -16.1\ kJ\ mol^{-1}$). Eventually, such compensating behavior of incremental enthalpy and entropy (spermine versus propylammonium) leads to the virtually identical affinity enhancement of 14–16 times for both guests in 0.2 M LiCl solution.

To the best of our knowledge, the stability of spermine-CB[6] complex as large as $5.4 \times 10^{10}\ M^{-1}$ obtained in 0.2 M LiCl solution is the highest reported in the literature for any known complexes of CB[6] macrocycle under any conditions.

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