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Intermolecular complexation thermodynamics between water-soluble calix[4]arenes and diazacycloalkanes

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Abstract

Calorimetric titration experiments have been performed in pH 2.0 and 7.2 phosphate buffer solutions at 298.15 K to calculate the complex stability constants (K_S) and thermodynamic parameters (ΔG°, ΔH°, and $T\Delta S^\circ$) for the stoichiometric 1:1 inclusion complexation of water-soluble calix[4]arene tetrasulfonate (CAS) and thiacalix[4]arene tetrasulfonate (TCAS) with some diazacycloalkane guests, i.e. piperazine (**1**), homopiperazine (**2**) and 1,5-diazacyclooctane (**3**). The results indicated that complexes of CAS and TCAS with diazacycloalkane guests were enthalpy-stabilized, and an acidic environment was more favorable to host–guest complexation than a neutral one. CAS forms more stable complexes with guest molecules than TCAS due to the more favorable enthalpic gain.

Keywords: Calixarene; Microcalorimetric titration; Supramolecular chemistry; Thermodynamics

1. Introduction

Possessing hydrophobic cavities made of several phenolic units linked via methylene groups [1,2], calixarenes and their derivatives form host–guest complexes with a wide variety of organic/inorganic/ionic guests. Much effort has been devoted to ionic/molecular recognition by calixarenes in organic solvents [3], but corresponding studies in aqueous solution are limited, due to the poor water solubility of calixarenes, to complexes of water-soluble *p*-sulfonatocalix[*n*]arenes ($n = 4$, 6 and 8) with some positively charged organic ammonium cations [4–6], amphoteric amino acid/polypeptides [7–9], mono-substituted benzenes [10], and organic dyes [11,12]. These results reveal that several weak intermolecular interactions cooperatively contribute to inclusion complexation by calixarenes, and the size/shape-fit relationship between host and guest is the main factor governing the molecular recognition ability. The present paper reports data on the inclusion complexation thermodynamics of calix[4]arene tetrasulfonate (CAS) and thiacalix[4]arene tetrasulfonate (TCAS) with piperazine (**1**), homopiperazine (**2**) and 1,5-diazacyclooctane (**3**), in an acidic (pH = 2.0) or a neutral (pH = 7.2) aqueous solution (Scheme 1) to examine how the size-fit relationship and pH affect the binding ability of water-soluble calix[4]arenes.

2. Experimental

2.1. Materials

CAS and TCAS were synthesized according to the reported method [4c,13] and characterized by IR, NMR and elemental analysis. Piperazine and homopiperazine were purchased from Acros and used without any purification. 1,5-diazacyclooctane was synthesized according to the reported method [14]. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 mol dm^{-3} buffer solution (pH 7.2), while sodium dihydrogen phosphate was dissolved in distilled, deionized water to make a 0.1 mol dm^{-3} solution, which was then adjusted to pH 2.0 by phosphoric acid. The pH values of the obtained buffer solutions were verified on

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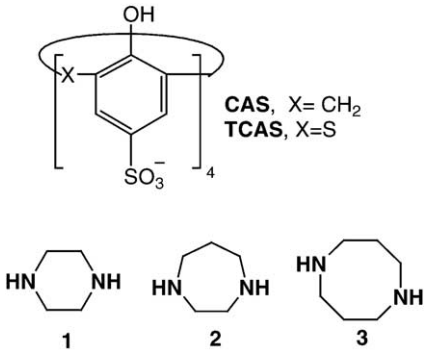

Scheme 1. Structures of hosts and guests.

a Sartorius pp-20 pH-meter calibrated with standard buffer solutions.

2.2. Isothermal calorimetric titration

Calorimetric titrations were performed with a VP-ITC from Microcal Inc., Northampton, MA. The calorimeter was calibrated chemically by performing the complexation reaction of β-cyclodextrin with cyclohexanol prior to use, which gave $\log K_S = 2.83 \pm 0.02$, $\Delta H^\circ = -6.51 \pm 0.03$ in good agreement with the literature data, $\log K_S = 2.85 \pm 0.01$, $\Delta H^\circ = -6.6 \pm 0.1$ [15]. All titrations were performed in aqueous phosphate buffer solution (pH = 7.2 or 2.0) at atmospheric pressure and 298.15 K. Each solution was degassed and thermostated with a ThermoVac accessory before the titration. In each run, 25 successive injections (10 μL/injection) of host solution (20.0 mM) were injected with stirring at 300 rpm into the reaction cell (1.4227 mL) charged with guest solution (1.0 mM) in the same buffer solution.

Since the dilution heat of calixarene was not negligible, the dilution heat was determined by injecting the host solution into a buffer solution without guest under the same condition. The dilution enthalpy was subtracted from the enthalpy measured in the titration experiment to obtain the net reaction heat.

ORIGIN software designed specifically for ITC data analysis (Microcal Inc.) was used to simultaneously compute equilibrium constant (K_S) and standard molar enthalpy of reaction (ΔH°) from each titration curve by fitting with the 'one set of binding sites' model. The model was fitted to the $\Delta Q(i)$ values for each injection by nonlinear least squares. The first point was excluded from the fitting procedure, but the titrant added in the first injection was included in calculating the total amount of titrant in the solution. A typical titration curve and fitting results for the complexation of CAS with piperazine at pH 7.2 are shown in Fig. 1. Two titration experiments were carried out and their average value used to calculate the complex stability constant and thermodynamic parameters. The obtained complex stability constant (K_S), standard free energy (ΔG°), enthalpy change (ΔH°), and entropy change ($T\Delta S^\circ$) for the host–guest inclusion complexation are listed in Table 1.

3. Results and discussion

It is widely reported that calix[4]arenes can form typical 1:1 complexes with model substrates. In our experiments, the titration data also gave the 1:1 binding stoichiometry with the

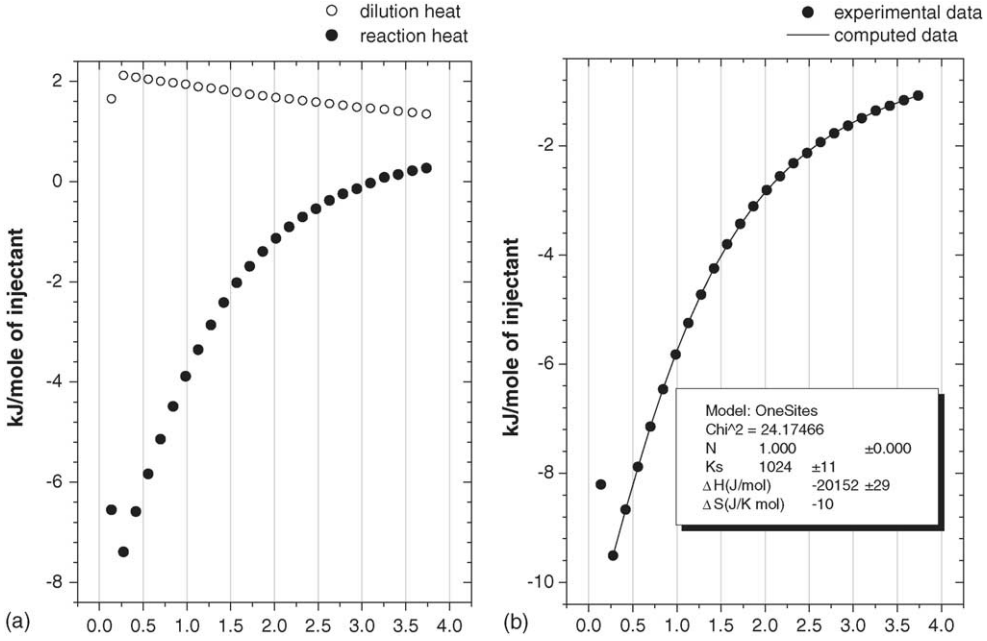

Fig. 1. (a) Heat effects of dilution and of complexation of CAS with piperazine for each injection during a titration. (b) 'Net' heat effects of complexation of CAS with piperazine for each injection, obtained by subtracting the dilution heat from the reaction heat, fitted by computer simulation using the 'one set of binding sites' model.

Table 1
Thermodynamic parameters for 1:1 complexation of guest molecules with CAS and TCAS in phosphate buffer solution (pH 7.2 and 2.0) at 298.15 K

Host (pH)	Guest	K_S (M^{-1})	ΔG° (kJ mol^{-1})	ΔH° (kJ mol^{-1})	$T\Delta S^\circ$ (kJ mol^{-1})
CAS (7.2)	**1**	1035 ± 10	−17.21 ± 0.02	−20.05 ± 0.12	−2.85 ± 0.15
	2	8538 ± 13	−22.44 ± 0.01	−26.40 ± 0.03	−3.96 ± 0.03
	3	10470 ± 73	−22.95 ± 0.01	−13.80 ± 0.01	9.15 ± 0.01
CAS (2.0)	**1**	893 ± 17	−16.85 ± 0.04	−9.13 ± 0.09	7.71 ± 0.16
	2	11750 ± 45	−23.23 ± 0.01	−20.32 ± 0.01	2.91 ± 0.01
	3	13775 ± 5	−23.63 ± 0.01	−17.48 ± 0.05	6.15 ± 0.05
TCAS (7.2)	**1**	[a]			
	2	243 ± 6	−13.62 ± 0.07	−16.00 ± 0.33	−2.80 ± 0.39
	3	[a]			
TCAS (2.0)	**1**	[a]			
	2	357 ± 17	−14.57 ± 0.13	−8.47 ± 0.21	6.10 ± 0.33
	3	346 ± 5	−14.50 ± 0.04	−7.95 ± 0.08	6.55 ± 0.12

[a] K_S or ΔH° was too small to be determined.

results varying from 0.93 to 1.16. Molecular model studies with the MM2 force field calculation were performed to give the optimized conformation of host–guest complex. The result clearly demonstrated that CAS or TCAS could only accommodate one guest in its hydrophobic cavity (Fig. 2). The UV spectra of host calixarenes in the absence and presence of guests confirms the occurrence of the inclusion complexation. Fig. 3 illustrates the UV spectra of CAS and without guest **3**. The absorbance of CAS gradually increased upon the addition of **3**. In the control experiment, the UV spectra of the monomer, 4-phenolsulfonic acid (sodium salt), did not show appreciable changes with the gradual addition of **3** under the same experimental conditions. These data indicate that the guest is included in the hydrophobic cavity of the host calixarene.

Except for **1**/CAS, both CAS and TCAS bound guest molecules more strongly in an acidic buffer (pH 2.0) than in a neutral one (pH 7.2). TCAS showed no complexation ability toward guest **3** in a neutral buffer solution (pH 7.2), but gave an appreciable K_S value in an acidic one (pH 2.0). The four sulfonate groups of the host calixarene exist as anions in both the acidic and neutral buffers [7b], so the enhanced binding is due to the stronger intermolecular interactions between the diazacycloalkane dications and calixarene at pH 2.0 [16] than with the mono-protonated species at pH 7.2.

The complexation of CAS/TCAS with guests **1**–**3** was driven by the favorable enthalpic changes, accompanying either positive or negative entropy changes. Evidence for the size-fit relationship between host and guest is the 'host selectivity'. CAS bound guests more strongly with more negative enthalpic changes than TCAS in either an acidic or a neutral buffer solution. CAS, with four methylene groups has a smaller cavity than TCAS, with four sulfur atoms [10], and apparently fits the size of diazacycloalkane guests better.

Evidence for the size-fit relationship between host and guest also comes from the 'guest selectivity'. Both the enthalpic ($-\Delta H^\circ$) and entropic ($-T\Delta S^\circ$) contributions decreased in the following order: at pH 7.2, for CAS: **2** > **1** > **3**; for TCAS: **2** > **1** = **3**; at pH 2.0, for CAS: **2** > **3** > **1**; for TCAS: **2** > **3** > **1**. That is, guest **2**, with the smallest ring size, gave the more negative enthalpic changes and the more unfavorable entropic changes than other guests upon complexation with host calixarenes. The more favorable enthalpic change

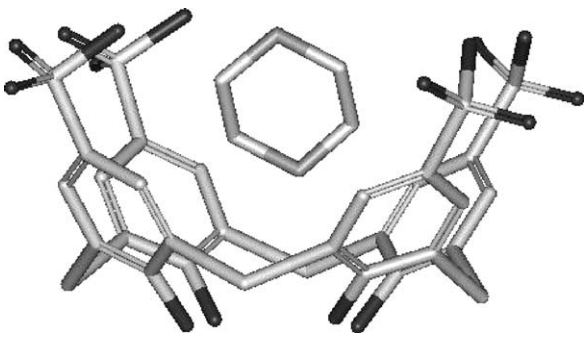

Fig. 2. MM2-opimized binding mode between TCAS and **1** (H atoms are omitted for clarity).

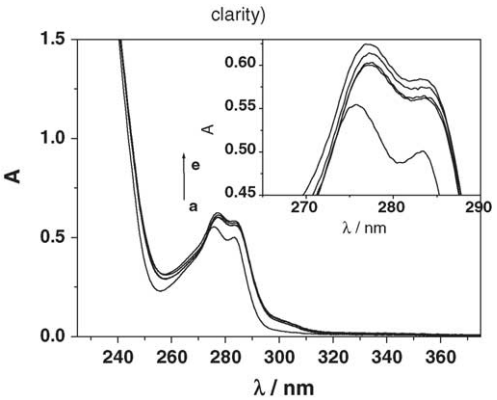

Fig. 3. UV–vis spectra of CAS (1×10^{-4} mol/L) in the presence of guest **3** ($0–30 \times 10^{-4}$ mol/L from a to e) in pH 2.0 phosphate buffer solution at 25.0 °C.

indicated that guest **2** was more suitably accommodated in the cavity of CAS (or TCAS) than the larger rings.

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