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PAPER

Thermodynamic origins of selective binding affinity between *p*-sulfonatocalix[4,5]arenes with biguanidiniums†

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The binding geometries, abilities and thermodynamic parameters for the intermolecular complexation of two water-soluble calixarenes, *p*-sulfonatocalix[4]arene (SC4A) and *p*-sulfonatocalix[5]arene (SC5A), with biguanidinium guests, metformin (MFM) and phenformin (PFM), were investigated by ^{1}H and 2D NMR spectroscopy, X-ray crystallography, and isothermal titration calorimetry (ITC). The obtained results show that biguanidinium guests are captured by calixarenes with the alkyl or aromatic portion immersed into the cavities and the guanidinium portion fixed at the upper-rims. At both acidic and neutral conditions, SC4A always presents stronger binding affinities to biguanidinium guests than SC5A. Moreover, SC4A prefers to include MFM rather than PFM. As a result, the binding selectivity of MFM is up to 44.7 times for the SC4A/SC5A hosts. The intrinsic relationship between binding structures and selectivities were comprehensively analyzed and discussed from the viewpoint of thermodynamics. Finally, the ITC measurements were further performed in phosphate buffer instead of aqueous solution, to examine the buffer effects, counterion effect, and the differences between thermodynamic and apparent association constants.

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Introduction

p-Sulfonatocalix[*n*]arenes (SC*n*As, *n* = 4–8),[1] a family of water-soluble calixarene derivatives, have gained considerable attention in the fields of molecular recognition/sensing,[2] crystal engineering,[3] catalysis,[4] amphiphiles,[5] enzyme-mimics/enzyme-assays,[6] and medicinal chemistry.[7] The diverse applications result from their outstanding binding properties. Possessing three-dimensional, flexible, π-electron rich cavities, SC*n*As are able to complex with numerous guest molecules, including inorganic cations,[8] organic ammonium cations,[9] pyridiniums/viologens,[10] neutral organic molecules,[11] dyes,[12] and bio-relevant molecules.[13] It is worth noting that the strong binding affinity of SC*n*As and high molecular selectivity towards organic cations is driven by the synergistic effect of additional anchoring points donated by sulfonate groups together with the intrinsic cavities. A lot of effort has been devoted to the binding behaviors of SC*n*As with several kinds of organic cations, *e.g.*, primary ammoniums,[14] secondary ammoniums,[15] quaternary ammoniums,[2c,9b,9c] pyridiniums,[10] and metal-coordinates.[16] Surprisingly, one noticeable kind of organic and biological cation, the guanidine salts, have been paid less attention regarding their inclusion phenomena with SC*n*As. Morel-Desrosiers and co-workers measured the binding stability and thermodynamic origin of SC*n*As with arginine, which bears a guanidinium end-group.[13a,b] The complexation of SC4A with some simple alkyl-appended guanidiniums was also reported by the same group.[17] Therefore, as part of our ongoing program concerning the supramolecular chemistry of SC*n*A macrocycles, we decided to study the binding behaviors of SC*n*As toward biguanidiniums herein, which will be helpful to understand the molecular recognition of SC*n*As more systematically and comprehensively.

Two smaller host analogues (Scheme 1), SC4A and SC5A, were selected for their relatively stable pre-organized cone shapes, while the other larger ones are always conformationally susceptible.[3c] Biguanidiniums, metformin (MFM) and phenformin (PFM), were employed as model guest molecules. These guests are important for treatment of hyperglycemia in patients with noninsulin-dependent diabetes mellitus.[18] The host–guest binding structures, stabilities and thermodynamic origins were evaluated by means of NMR spectroscopy, X-ray crystallography, and isothermal titration calorimetry (ITC). In view of the pH-sensitivity of both hosts and guests, all the experiments were performed at acidic and neutral conditions, respectively. Moreover, the counterion-dependent binding of SC*n*As has been proved by competitive fluorophore displacement and ^{23}Na relaxation NMR measurements where SC4A has been shown to bind

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†Electronic supplementary information (ESI) available: $\Delta\delta$ values of MFM and PFM upon complexation with SC4A or SC5A at pD 2.0 and 7.2; NMR spectra of MFM⊂SC4A, PFM⊂SC4A, and MFM⊂SC5A; the other alternative inclusion structure of MFM⊂SC4A. CCDC reference numbers 820613–820615. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06313a

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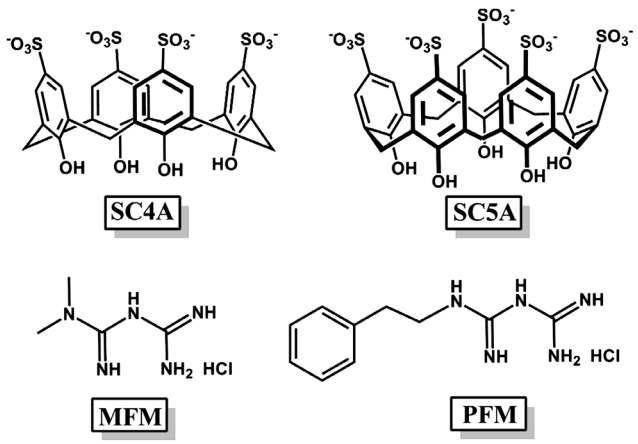

Scheme 1 Structures of the SC*n*A hosts and guanidinium guests.

Na^+ with the binding constant of about 85–100 M^{-1}.[8c,19] However, no significant heat effect was detected for Na^+ with SC4A by ITC measurement, possibly due to that ITC technique is intrinsically unsuitable for thermoneutral, *i.e.*, purely entropy-driven complexations. As a result, we performed the ITC measurements in aqueous solution and phosphate buffer, respectively, to examine the dependence of binding on different pH and in ionic conditions with respect to the thermodynamic parameters involved.

Results and discussion

Binding geometries in solution

The formation of inclusion complexes between SC*n*As and guanidiniums is clearly evident in ^{1}H NMR spectroscopic experiments in D_2O (Fig. 1 and Fig. 2). In the presence of about 0.5–3.0 equiv. of SC*n*As, all the protons of MFM and PFM exhibit a visible upfield shift ($\Delta\delta$) owing to the ring current effect of the aromatic nuclei of calixarenes,[9c] which suggests that the guanidinium guests are encapsulated into the SC*n*A cavities. The $\Delta\delta$ value for each proton is different, which can be used as a powerful evidence to deduce the host–guest binding geometry. For MFM guest, there is only one kind of methyl proton to be traced, and for PFM, 5 kinds of protons to be traced. In the PFM case, upon addition of SC4A in both acidic (pD 2.0) and neutral (pD 7.2) D_2O solution, the $\Delta\delta$ values are in the order of $H_a > H_b > H_c \geq H_d > H_e$; upon addition of SC5A, the $\Delta\delta$ values are in the order of $H_c > H_a \approx H_b \approx H_d > H_e$, pD 2.0; $H_c > H_d > H_a \approx H_b \approx H_e$, pD 7.2 (Table S2†). It indicates that PFM is immersed into the SC4A cavity in its longitudinal orientation with the benzene group being included first. SC5A possesses similar cone shape to SC4A, but with a wider size.[10e] As a result, the SC5A cavity can accommodate guest molecules in more latitudinal orientation.[9c,10c,10e] The inclusion structure of SC5A with PFM was further identified by 2D ROESY spectrum (Fig. 3). All the five protons of PFM present clear cross-peaks with the aromatic proton of SC5A, where the cross-peak of H_a with calixarene proton is relatively weaker than the others. Moreover, taking the expected electrostatic and hydrogen-bonding interactions between positive guanidinium groups and negative sulfonate groups into account, we inferred the binding geometries of SC*n*As with MFM and PFM as shown in Scheme 2. In all cases, the alkyl and aromatic portions of MFM and PFM are included into the hydrophobic cavities of calixarenes, and the biguanidinium portion is fixed at the upper-rim, captured by the sulfonate groups. PFM would undergo somewhat structural distortion to be concurrently included by the cavity and captured by the sulfonate anchoring points. It should be mentioned here that the protonation states are different at acidic and neutral conditions, two-positive charges forms for both MFM and PFM at pD 2.0, and one-positive charge forms at pD 7.2. However, since it does not lead to obvious difference of binding manner, the protonation states of MFM and PFM are not marked in Scheme 2.

It is well-known that SC4A and SC5A adopt the cone conformation with all of the phenolic oxygen atoms in an approximate plane, and there is no compromise arising from any preorganization energy required for the binding of hydrophobic moieties

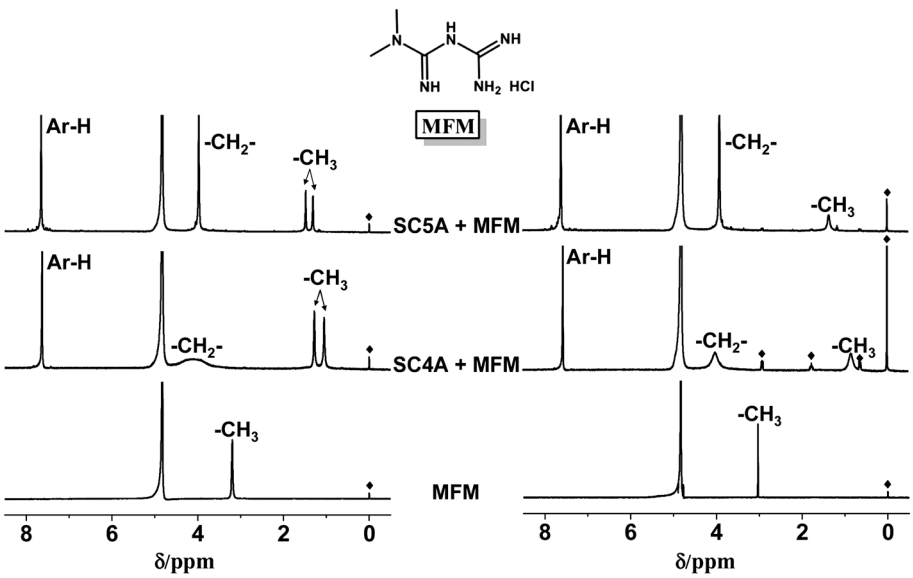

Fig. 1 The ^{1}H NMR spectra of MFM in the absence and presence of SC4A or SC5A at pD 2.0 (left) and pD 7.2 (right). ("♦" represents DSS signals.).

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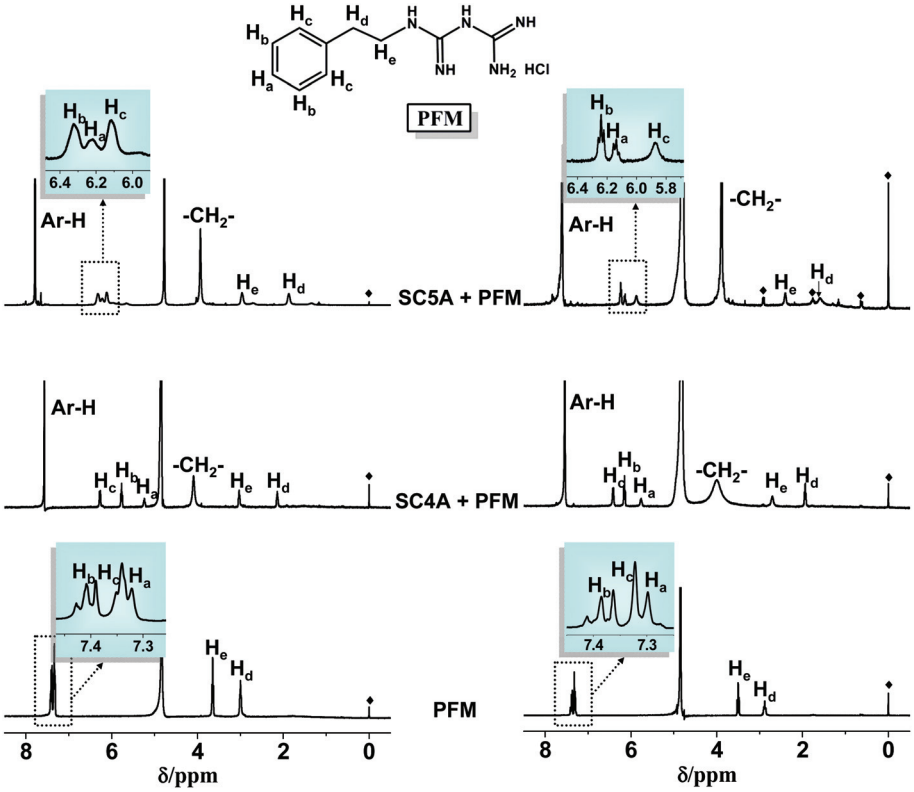


Fig. 2 The ^{1}H NMR spectra of PFM in the absence and presence of SC4A or SC5A at pD 2.0 (left) and pD 7.2 (right). Some signals of guest protons were assigned according to 2D NMR spectra. ("◆" represents DSS signals.).

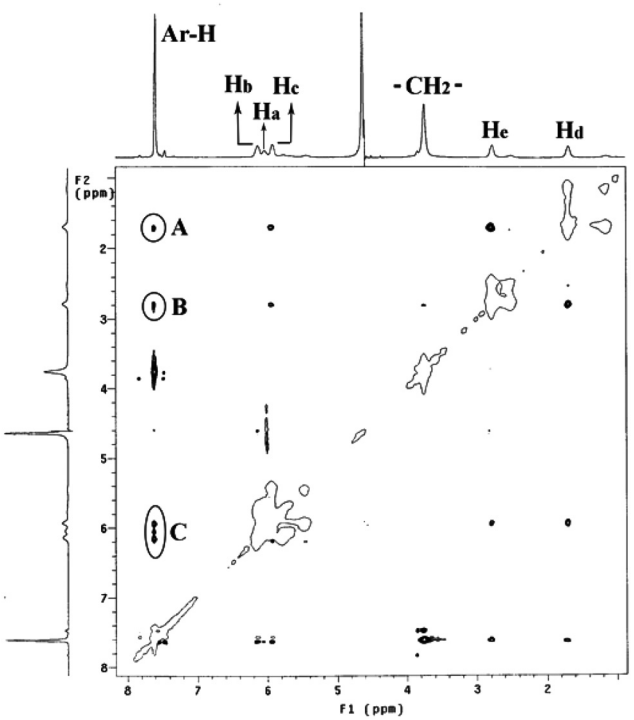
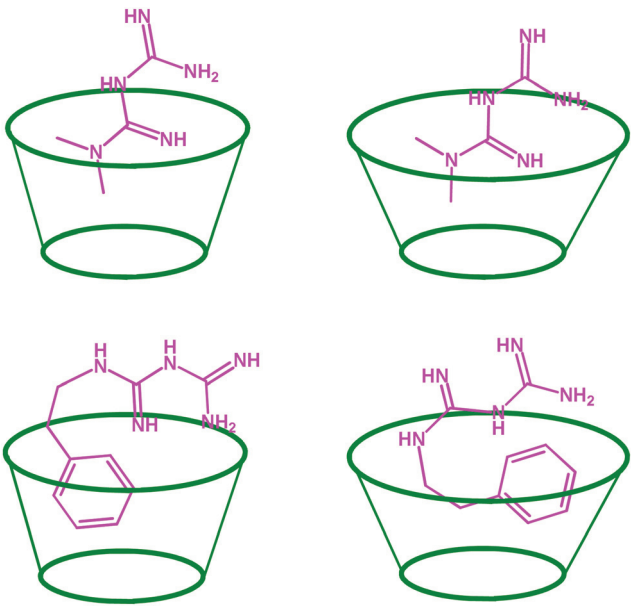


Fig. 3 The 2D ROESY spectrum of SC5A with PFM at pD 2.0 with a mixing time of 250 ms.



Scheme 2 The deduced binding geometries of SC4A (left) and SC5A (right) with MFM and PFM according to ^{1}H NMR spectra, as well as 2D ROESY spectrum.

with their cavities.[3c,10c] No appreciable resonance shift for calixarene protons is observed before and after complexation, but the bridged methylene signals of SC4A broaden to baseline upon complexation with MFM and PFM. This phenomenon provides the evidence for a conformational rigidification of SC4A. The methylene signals of SC5A retain their original sharp shape, therefore the conformation of SC5A is not compromised by

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accommodating MFM and PFM guests. The distinguishable conformational freedoms between SC4A and SC5A are reflected in the aforementioned thermodynamic parameters of the entropy term.

Binding structures in solid state

Three single-crystal complexes of SC*n*As with biguanidinium guests, MFM⊂SC4A, PFM⊂SC4A, MFM⊂SC5A, were obtained under acidic conditions.[20] Their molecular structures have been determined by single-crystal X-ray diffraction analyses. Complexes MFM⊂SC4A, PFM⊂SC4A, MFM⊂SC5A crystallize in the monoclinic space group *Cc*, the monoclinic space group $P2_1/n$, and the monoclinic space group $P2_1/c$, respectively. In the asymmetric unit, there are two crystallographically distinct SC4A, four MFM, and 18.25 water molecules for MFM⊂SC4A; one SC4A, two PFM, and 8.5 water molecules for PFM⊂SC4A; one SC5A, two and a half MFM, and 12 water molecules for MFM⊂SC5A, respectively. Among these three crystals, some sulfonate groups of SC*n*As and several water molecules disorder at two or more positions. The present crystal structures are different from the reported complexes of SC4A with guanidinium, where guanidinium molecules locate at the edge of calixarene upper-rim, forming merely hydrogen bonds with the sulfonate groups.[21] MFM and PFM possess not only biguanidinium group but also methyl and phenylethyl substituents, and therefore, SC*n*As prefer to complex them in the manner, where the methyl or phenylethyl group is included into the cavity with the biguanidinium group fixed at the upper-rim.

In complex MFM⊂SC4A, there are two kinds of host–guest inclusion structures, possibly owing to the solid-state aggregation. Only one is discussed here, while the other is found in the ESI† (Fig. S4). One MFM guest penetrates into the SC4A cavity with a slantwise orientation (Fig. 4), while the other acts as counterion located in the crystal lattice. The methyl groups of MFM are captured into the cavity of SC4A *via* two C–H···π interactions (C63–H63···ring of C36–41, 2.726(1) Å, 150.4(5)°; C64–H64···ring of C50–55, 3.617(1) Å, 146.7(5)°), while the positive guanidinium group is fixed at the upper-rim of SC4A, captured by two sulfonate groups *via* two hydrogen bonds (N6···O21, 2.824(9) Å, 147.0(5)°; N7···O30, 2.836(9) Å, 150.4 (5)°). We noticed that two methyl groups are different in terms of both the host–guest interaction and inclusion depth. This may help us understand the unexpected NMR phenomena of MFM⊂SC4A complex at pD 2.0. The resonance of methyl groups of MFM splits from one peak to two peaks when included by SC4A. One reasonable explanation is that the chemical environments of two methyl groups of free MFM are same, whereas upon complexation with SC4A, the chemical environments become different according to the solid-state binding structures, and therefore, the complexed MFM exhibits two distinct resonance signals. So it is in the MFM⊂SC5A case.

In complex PFM⊂SC4A, one PFM guest is bound in the SC4A cavity, the other one acts as counterion in the crystal lattice. The aromatic moiety of PFM penetrates into the SC4A cavity at 74.4(2)° to a depth of 4.245(6) Å.[22] The immersion of aromatic moiety of PFM is contributed to three C–H···π interactions (C29–H29···ring of C23–28, 3.156(1) Å, 121.1(4)°; C30–H30···ring of C16–21, 3.547(1) Å, 111.8(4)°; C31–H31···ring of C9–14, 3.033(2) Å, 118.9(4)°), while the positive guanidinium group is fixed at the upper-rim of SC4A, captured by sulfonate groups through two hydrogen bonds (N3···O14, 2.743(6) Å, 159.5(3)°; N4···O12, 2.835(5) Å, 157.8(3)°) (Fig. 5). On the other hand, the guest-induced conformational perturbations of calixarenes are different between complexes MFM⊂SC4A and PFM⊂SC4A. In MFM⊂SC4A, SC4A shows the cone shape of C_{2v} symmetry with sulfur distances of 11.850 (3) Å and 8.519(3) Å for oppositely oriented sulfonate groups. In PFM⊂SC4A, SC4A shows C_{4v} cone shape with sulfur distances of 11.086(2) Å and 11.000(3) Å. Moreover, the actual ϕ and χ torsion angle values, which are used to define the solid-state conformation of calixarenes according to the Ugozzoli–Andreetti convention,[23] are 100.3(8), −81.1(8); 81.9(7), −101.8 (7); 101.1(7), −75.6(7); 75.9(8), −102.2(8) for MFM⊂SC4A and 95.9(6), −92.6(1); 91.9(6), −90.6(1); 93.9(6), −93.8(6); 92.5(6), −94.0(6) for PFM⊂SC4A, respectively.

In complex MFM⊂SC5A, one MFM guest is bound into the SC5A cavity, while the others act as counterions in the crystal lattice. The methyl groups of MFM are immersed into the calixarene cavity *via* two C–H···π interactions (C38–H38···ring of C29–34, 2.546(1) Å, 165.6(1)°; C39–H39···ring of C8–13, 2.969(1) Å, 148.5(1)°) while the positive guanidinium group is fixed at the upper-rim of SC5A, captured by two sulfonate groups through two hydrogen bonds (N1···O18, 2.855(4) Å, 151.0(4.0)°; N2···O12, 2.896(3) Å, 165.0(4.0)°) (Fig. 6). We notice that MFM penetrates into the SC5A cavity to a deeper depth than SC4A which can be reflected from the distances between the methyl carbon atoms of MFM and the planes of the calixarene CH_2 carbon atoms. The distances involved in complex MFM⊂SC5A are 1.626(3) Å and 3.712(3) Å, which are shorter than 3.524(8) Å and 4.630(8) Å involved in complex

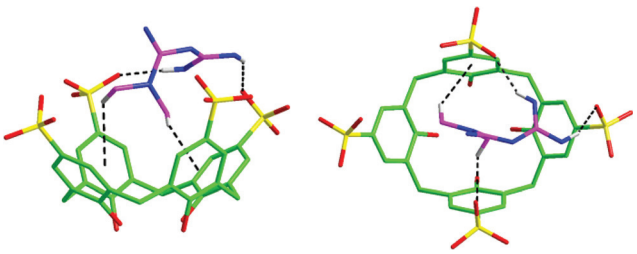

Fig. 4 Solid-state inclusion structure of MFM⊂SC4A. The broken lines represent the intermolecular hydrogen bonds or the C–H···π interactions between host and guest.

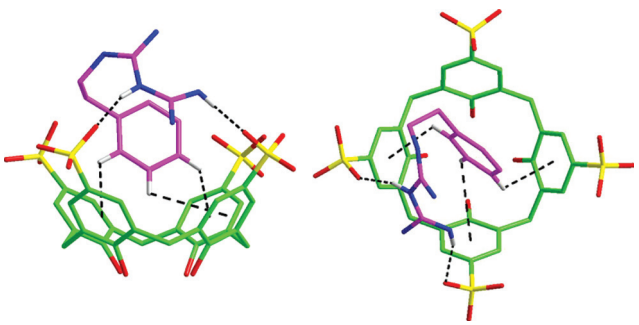

Fig. 5 Solid-state inclusion structure of PFM⊂SC4A. The broken lines represent the intermolecular hydrogen bonds or the C–H···π interactions between the host and the guest.

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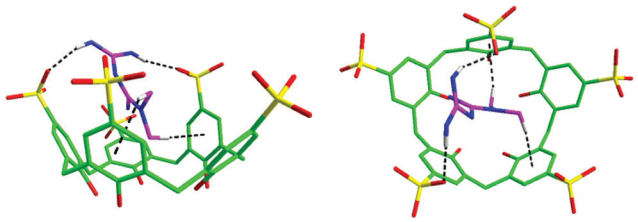

Fig. 6 Solid-state inclusion structure of MFM⊂SC5A. The broken lines represent the intermolecular hydrogen bonds or the C–H···π interactions between host and guest.

MFM⊂SC4A. Owing to the immersion of MFM, the pinched symmetry can be observed in SC5A, as shown by the actual ϕ and χ torsion angle values: 80.8(3), −56.5(3); 86.9(3), −88.4(3); 71.9(3), −93.0(3); 100.0(3), −54.0(3); 68.6(3), −108.0(3).

Binding stabilities and thermodynamics

To determine quantitatively the inclusion complexation behaviors of SC*n*As with the biguanidinium guests, ITC measurements were performed at acidic and neutral conditions, respectively, which is a powerful tool for determining the host–guest complex interactions, because it not only gives the complex stability constants (K_S), but also yields their thermodynamic parameters (enthalpy and entropy changes $\Delta H°$, $\Delta S°$). The data obtained are listed in Table 1. In all present cases, the titration data could be well fitted by computer simulation using the "one set of binding sites" model and repeated as 1 : 1 complex formation, such that higher-order complexes did not need to be postulated.

As can be seen from Table 1, both SC4A and SC5A can form stable complexes with biguanidinium guests (K_S = 10^3 to 10^5 M^{-1}), where the complexation of SC4A is mainly driven by the enthalpy changes accompanied with minor either favorable or unfavorable entropy changes, the complexation of SC5A is synergistically contributed by both the enthalpy and entropy changes. It has been well documented that, among several noncovalent interactions working between host and guest, the charge, hydrogen bond, π···π, C–H···π, and van der Waals interactions contribute to the enthalpy changes, while the conformational change and the desolvation effect contribute the entropy changes.[13a] From the above crystal results, C–H···π interactions between the methyl groups in MFM (benzene group in PFM) and the aromatic cavities of calixarenes, charge interactions and hydrogen bonds between guanidinium groups and sulfoante groups are the dominantly driving forces that leading to exothermic enthalpy changes ($\Delta H°$ = −9.10 to −28.40 kJ mol^{-1}) in the host–guest complexation. The desolvation effect between positive-charge guanidinium groups and negative-charge sulfonate groups leads to positive entropy values, while the loss of conformational degrees of freedom for the hosts and structural freezing upon complexation lead to negative entropy values. In the SC5A cases, all the entropy terms are favorable ($T\Delta S°$ = 5.68 to 9.82 kJ mol^{-1}), indicating that the conformational loss is less effective than the desolvation effect. In the SC4A cases, three of four data are unfavorable ($T\Delta S°$ = −1.16 to −6.20 kJ mol^{-1}), indicating that the desolvation effect can not compensate the loss of conformational freedom.

Table 1 Complex stability constants (K_S/M^{-1}), enthalpy ($\Delta H°$/kJ mol^{-1}) and entropy changes ($T\Delta S°$/kJ mol^{-1}) for 1 : 1 intermolecular complexation of SC*n*As with MFM and PFM in aqueous solution (pH 2.0 and 7.2) at 298.15 K

Hosts	Guests	pH	lgK_S	$\Delta H°$	$T\Delta S°$
SC4A	MFM	7.2	3.84 ± 0.01	−22.99 ± 0.13	−1.16 ± 0.13
		2.0	5.22 ± 0.02	−26.70 ± 0.10	3.00 ± 0.17
	PFM	7.2	3.31 ± 0.01	−25.04 ± 0.15	−6.20 ± 0.17
		2.0	4.45 ± 0.02	−28.40 ± 0.21	−3.02 ± 0.26
SC5A	MFM	7.2	3.14 ± 0.02	−12.18 ± 0.10	5.68 ± 0.04
		2.0	3.57 ± 0.01	−10.50 ± 0.04	9.82 ± 0.03
	PFM	7.2	3.11 ± 0.02	−9.10 ± 0.08	8.65 ± 0.10
		2.0	4.17 ± 0.01	−15.76 ± 0.04	8.00 ± 0.06

Comparing the K_S values between pH 2.0 and 7.2, we found that SC*n*As always presents stronger binding affinities for biguanidinium guests in acidic aqueous solution than in neutral solution, although the calixarene cavities at pH 7.2 possess higher π-electron density than those at pH 2.0, and can afford stronger π···π and C–H···π interactions.[10e,11e] This originates mainly from the protonation states of biguanidinium guests. According to their pK_a values,[24] MFM and PFM exist in mono-protonated form at pH 7.2, and mainly in di-protonated form at pH 2.0. Two factors contribute to the higher complex stabilities for di-protonated biguanidiniums than mono-protonated biguanidiniums: one is that di-protonated biguanidinium groups show more advantage to form charge interactions and hydrogen bonds with sulfonate groups of SC*n*As than mono-protonated biguanidinium groups, reflected from the enthalpy changes; the other is that the desolvation effect between di-protonated biguanidinium groups and sulfonate groups is more extensive than that of mono-protonated biguanidinium groups, reflected from the entropy changes. Taking the SC4A+MFM case as example, the K_S value at pH 2.0 is 24 times higher than that at pH 7.2, resulting from both the more favorable enthalpy change ($\Delta\Delta H°$ = −3.71 kJ mol^{-1}) and entropy change ($T\Delta\Delta S°$ = 4.16 kJ mol^{-1}).

For either MFM or PFM guests, SC4A presents stronger binding affinities than SC5A, and the host selectivities are in the range from 1.6 to 44.7 times. SC4A possesses more compact framework and higher π-electron density of cavity than SC5A,[10c] and also, the size/shape fit between SC4A and biguanidiniums is better than SC5A, which leads to more effective host–guest interactions of SC4A. It can be clearly seen from the enthalpy term that the enthalpy changes of SC4A upon complexation with MFM and PFM are almost two times larger than those of SC5A. But the complexation of SC4A is much more unfavorable than SC5A in terms of entropy change. This originates the large loss of conformational degree of freedom for SC4A. Such more pronounced complex-induced structure freezing of SC4A is also validated by the aforementioned NMR results. It is noteworthy that the host selectivities of MFM are several times larger those of PFM, and especially, the host selectivity (SC4A/SC5A) of MFM at pH 2.0 is 44.7 times higher, while the host selectivity of PFM at the same condition is only 1.9 times. We considered it is on account of the factor of guest sizes. SC4A prefers to accommodate the smaller MFM to a great extent. In this context, it is necessary to discuss the guest selectivities in detail.

SC4A encapsulates MFM stronger than PFM at both acidic and neutral conditions. Typically, the guest (MFM/PFM)

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selectivity of SC4A is 5.8 times at pH 2.0. Thermodynamically, the entropy changes of SC4A with MFM are more favorable than those with PFM ($T\Delta\Delta S°$ = 5.04 and 6.02 kJ mol^{-1}), while the enthalpy changes of SC4A with MFM are somewhat less favorable than those with PFM ($\Delta\Delta H°$ = 2.05 and 1.70 kJ mol^{-1}). Possessing an aromatic benzene substituent, PFM is more suitable to be included into the π-rich cavity of calixarene than MFM, forming host–guest interactions contributed to the enthalpy term. On the other hand, PFM is larger in size than MFM, and therefore, SC4A would suffer more loss of conformational degree of freedom upon complexation with PFM than MFM. We thus noticed that the guest selectivities of SC4A are dramatically governed by the entropy changes, although the complexation processes are driven by the enthalpy changes. These results indicate that the larger enthalpy changes do not always mean higher complex stabilities. At pH 7.2, SC5A almost shows no selectivity for the MFM/PFM pairs. At pH 2.0, SC5A shows reversed guest selectivity to SC4A, where the binding constant with PFM is 4.0 times larger than that with MFM, indicating that SC5A with its larger cavity size is a better receptor to accommodate PFM than MFM. The thermodynamic origin of guest selectivity of SC5A is also different from that of SC4A. At pH 2.0, SC5A can bind PFM stronger than MFM, absolutely contributed by the enthalpy changes ($\Delta\Delta H°$ = −5.26 kJ mol^{-1}).

We further performed the ITC measurements in 0.1 M phosphate buffer solution to evaluate how and to what extent the buffer affects the host–guest binding between SC*n*As and biguanidinium guests. As can be seen from Table 2, the host–guest complex stabilities in buffer are obviously reduced as comparison with those in water. Such reduction should be discussed from the aspects of not only host but also guest. For SC*n*A hosts, they show weak binding affinities for Na^+. We calculated the complex stability constants of SC4A and SC5A with Na^+ are 85 ± 15 and 173 ± 18 M^{-1}, respectively, according to our previous data of competitive titrations.[6h] The concentration of Na^+ is about 0.17 M in 0.1 M phosphate buffer solution, and therefore, Na^+ will interfere with the complexation of SC*n*As to biguanidiniums although their binding affinities are weak. For biguanidinium guests, they may interact with the phosphate anions (0.1 M) *via* electrostatic forces, further affecting the host–guest complexation. For the same reason, Morel-Desrosiers and co-workers controlled the pH by using NaOH instead of a phosphate buffer in order to avoid any interference of the buffer with the guanidinium substrates.[17] Both the host and guest interferences are mainly originated from the entropy term, and the complex entropy changes in phosphate buffer are quite unfavorable than those in water. Moreover, during the course of host–guest complexation, the methyl and phenylethyl groups in and MFM and PFM enter into the calixarene cavities from water or 0.1 M phosphate buffer. That is, the initial chemical environments are different, which would also lead to distinguishable complex stability constants, enthalpy and entropy changes in phosphate buffer and aqueous solutions. Consequently, measuring binding constants of SC*n*As with guests (in particular with ionic guests) in ion buffers will make the host–guest complexation complicated (the effects of competing ions), and cannot reflect the real association constants unless assuming a competitive binding model.

Table 2 Complex stability constants (K_S/M^{-1}), enthalpy ($\Delta H°$/kJ mol^{-1}) and entropy changes ($T\Delta S°$/kJ mol^{-1}) for 1 : 1 intermolecular complexation of SC*n*As with MFM and PFM in 0.1 M phosphate buffer solution (pH 2.0 and 7.2) at 298.15 K

Hosts	Guests	pH	lgK_S	$\Delta H°$	$T\Delta S°$
SC4A	MFM	7.2	3.08 ± 0.01	−26.15 ± 0.44	−8.57 ± 0.50
		2.0	4.27 ± 0.01	−24.94 ± 0.12	−0.62 ± 0.12
	PFM	7.2	2.49 ± 0.01	−26.45 ± 0.54	−12.25 ± 0.56
		2.0	3.51 ± 0.02	−27.70 ± 0.05	−7.69 ± 0.11
SC5A	MFM	7.2	2.65 ± 0.02	−18.76 ± 1.12	−3.63 ± 1.21
		2.0	2.61 ± 0.01	−14.90 ± 1.01	−0.05 ± 0.01
	PFM	7.2	2.62 ± 0.02	−15.82 ± 0.39	−0.91 ± 0.44
		2.0	3.16 ± 0.02	−16.98 ± 0.22	1.08 ± 0.32

Conclusion

In conclusion, the binding behaviors of SC4A and SC5A with biguanidiniums MFM and PFM were systemically investigated in both aqueous solution and solid sate. The binding affinities depend on the size of calixarene cavity, guest substituents, as well as pH. Both SC4A and SC5A can provide stronger binding affinities at pH 2.0 than 7.2. SC4A is a better receptor than SC5A for the same substrate. SC4A can bind MFM much more tightly than PFM. As a result, SC4A presents the highest complex constant to MFM at pH 2.0, up to 10^5 M^{-1}. Thermodynamically, the complexation of SC4A with biguanidiniums is dominantly driven by the enthalpy changes, while the complexation of SC5A is driven almost equally by the enthalpy and entropy changes. Moreover, the ITC measurements in phosphate buffer show that the complexation of SC*n*As with guests is seriously influenced by surrounding ions. Great care should be taken when analyzing and discussing the binding behaviour in buffer. The apparent association constants by a simple titration model would be quite different from those by a competitive binding model. The present results will serve us to understand the inclusion phenomena, recognition mechanism, and thermodynamic origins of SC*n*As more systematically and comprehensively.

Experimental

Materials

The host molecules, *p*-sulfonatocalix[4]arene (SC4A)[25] and *p*-sulfonatocalix[5]arene (SC5A)[26] were synthesized and purified according to the respective literature procedures. The guest molecules, metformin (MFM) and phenformin (PFM) were commercially available from Aladdin Reagent and Sigma–Aldrich, respectively. They were used without further purification.

pH 2.0 and pH 7.2 solutions were prepared with distilled, deionized water and adjusted with 1 M hydrochloric acid (HCl) or 1 M sodium hydroxide (NaOH) and verified on a pH meter calibrated with two standard buffer solutions. The phosphate buffer solution of pH 2.0 was prepared by dissolving sodium dihydrogen phosphate in distilled, deionized water to make a 0.1 M solution, which was then adjusted to pH 2.0 by phosphoric acid. The phosphate buffer solution of pH 7.2 was prepared by dissolving disodium hydrogen phosphate ($Na_2HPO_4·12H_2O$,

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25.79 g) and sodium dihydrogen phosphate ($NaH_2PO_4{\cdot}2H_2O$, 4.37 g) in distilled, deionized water (1000 ml) to make a 0.1 M solution. D_2O was adjusted to pD 2.0 and pD 7.2 with 1 M DCl and 1 M NaOD. The value was verified on a pH meter calibrated with two standard buffer solutions. pH readings were converted to pD by adding 0.4 units.[27]

Preparation of complexes

Preparation of MFM⊂SC4A. MFM (2 equiv) was added to an aqueous solution of SC4A (26.6 mg, 12 mL). Precipitates were formed as the solution was stirred and adjusted to pH ≈ 2 by adding 1 M HCl dropwise. Consequently, the solution was heated until clear. After that, it was stirred for another 4 h at room temperature and filtered. The filtrate was left to evaporate for about one day. The colorless crystal that formed was collected along with its mother liquor for X-ray crystallographic analysis. ^{1}H NMR (400 MHz, D_2O, 298 K) δ 7.44 (8H, ArH, s), 4.27 (4H, $ArCH_2Ar$, br s), 3.51 (4H, $ArCH_2Ar$, br s), 1.93 (12H, CH_3, s).

Preparation of PFM⊂SC4A. PFM (2 equiv) was added to an aqueous solution of SC4A (25.8 mg, 35 mL). Precipitates were formed as the solution was stirred and adjusted to pH ≈ 2 by adding 1 M HCl dropwise. Consequently, the solution was heated until clear. After that, it was stirred for another 4 h at room temperature and filtered. The filtrate was left to evaporate for about two weeks. The colorless crystal that formed was collected along with its mother liquor for X-ray crystallographic analysis. ^{1}H NMR (400 MHz, D_2O, 298 K) δ 7.40 (8H, ArH, s), 6.69 (8H, ArH, br s), 6.45 (2H, ArH, br s), 3.88 (8H, $ArCH_2Ar$, s), 2.93 (4H, $–CH_2–NH$, br s), 2.21 (4H, $Ar–CH_2–$, br s). The peaks of PFM protons do not split well as a result of fast-exchange complexation between SC4A and PFM.

Preparation of MFM⊂SC5A. MFM (2.5 equiv) was added to an aqueous solution of SC5A (24.9 mg, 10 mL). Precipitates were formed as the solution was stirred and adjusted to pH ≈ 2 by adding 1 M HCl dropwise. Consequently, the solution was heated until clear. After that, it was stirred for another 4 h at room temperature and filtered. The filtrate was left to evaporate for about three weeks. The colorless crystal that formed was collected along with its mother liquor for X-ray crystallographic analysis. ^{1}H NMR (400 MHz, D_2O, 298 K) δ 7.54 (10H, ArH, s), 3.86 (10H, $ArCH_2Ar$, s), 2.35 (15H, CH_3, s).

Measurements

^{1}H and 2D NMR spectra were recorded on Brucker AV400 and Varian Mercury VX300 spectrometer, respectively. Chemical shifts (δ, ppm) in water were externally referenced to 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in order to avoid any possible interaction with *p*-sulfonatocalixarene hosts as well as with the biguanidinium guests. SC5A and PFM were mixed at 10.06 mM and 20.03 mM respectively, for their 2D ROESY and ^{1}H NMR experiments (pD 2.0). All the other hosts and guests were mixed in the molar ratios of about 0.5–3.0 : 1, with the guests' concentrations at 2.02–4.03 mM. ^{1}H NMR spectra of single-crystal complexes, MFM⊂SC4A, PFM⊂SC4A and MFM⊂SC5A were recorded in D_2O on Bruker AV400 spectrometer without adding DSS for clarity.

The X-ray intensity data for MFM⊂SC4A and MFM⊂SC5A were collected on a Rigaku MM-007 rotating anode diffractometer equipped with a Saturn724 CCD Area Detector System, using monochromated Mo-Ka (λ = 0.71075 Å)radiation at T = 113(2)K. Data collection and reduction were performed by program of Crystalclear–SM Expert 2.0 r2 (Rigaku, 2009). The X-ray intensity data for PFM⊂SC4A was collected on a Rigaku MM-007 rotating anode diffractometer equipped with a Saturn CCD Area Detector System, using monochromated Mo-Ka (λ = 0.71073 Å) radiation at T = 113(2)K. Data collection and reduction were performed by program of crystalclear (Rigaku/MSC Inc., 2005). All the three structures were solved by using direct method and refined, employing full-matrix least squares on F^2 (CrystalStructure, SHELXTL-97). The crystal structure data and details of structure refinements are listed in Table 3.

Table 3 Crystal structure data and details of structure refinements for MFM⊂SC4A, PFM⊂SC4A and MFM⊂SC5A

	MFM⊂SC4A	PFM⊂SC4A	MFM⊂SC5A
CCDC no.	820613	820614	820615
Formula	$C_{72}H_{128.5}N_{20}O_{50.25}S_8$	$C_{48}H_{71}N_{10}O_{24.50}S_4$	$C_{45}H_{81.5}N_{12.5}O_{32}S_5$
M_r/g mol^{-1}	2334.93	1308.39	1470.03
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*Cc*	$P2_1/n$	$P2_1/c$
a/Å	20.657(3)	15.129(3)	14.2990(17)
b/Å	18.786(3)	12.140(2)	20.408(2)
c/Å	26.624(4)	33.206(7)	22.893(2)
α (°)	90	90	90
β (°)	97.992(5)	100.51(3)	107.014(6)
γ (°)	90	90	90
V/Å^3	10231(3)	5997(2)	6388.2(12)
Z	4	4	4
ρ_c/g cm^{-3}	1.516	1.449	1.528
μ/mm^{-1}	0.281	0.248	0.283
F(000)	4922	2756	3100
Crystal size/mm	0.24 × 0.20 × 0.18	0.22 × 0.20 × 0.16	0.22 × 0.18 × 0.16
θ range [°]	1.47–26.00	1.60 – 25.02	1.79 – 27.91
Reflns collected/unique	41401/19429 [R_{int} = 0.0664]	36360/10489 [R_{int} = 0.1004]	50620/15220 [R_{int} = 0.0463]
GOF	1.068	1.070	1.184
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0881 wR_2 = 0.2120	R_1 = 0.1116 wR_2 = 0.2946	R_1 = 0.0655 wR_2 = 0.1504
R indices (all data)	R_1 = 0.1042 wR_2 = 0.2279	R_1 = 0.1352, wR_2 = 0.3058	R_1 = 0.0755 wR_2 = 0.1559

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Isothermal Titration Calorimetry (ITC)

A thermostated and fully computer-operated isothermal calorimetry (VP-ITC) instrument, purchased from Microcal Inc., Northampton, MA, was used for all microcalorimetric experiments. The VP-ITC instrument was calibrated chemically by measurement of the complexation reaction of β-cyclodextrin with cyclohexanol, and the obtained thermodynamic data were in good agreement (error < 2%) with the literature data,[28] and also by measurement of the complexation reaction of SC4A with methyl viologen, and the obtained thermodynamic data were in good agreement (error < 5%) with the literature data.[10e] All microcalorimetric titrations between calixarene hosts and guanidinium guests were performed in aqueous and phosphate buffer solutions (pH 2.0 or 7.2) at atmospheric pressure and 298.15 K. Each solution was degassed and thermostated by a ThermoVac accessory before the titration experiment. Twenty-five successive injections were made for each titration experiment. A constant volume (10 μL/injection) of host solution (3.51 – 18.52 mM) in a 0.250 mL syringe was injected into the reaction cell (1.4227 mL) charged with guest molecules solution (0.22 – 1.53 mM) in the same aqueous solution. A representative titration curve was shown in Fig. 7. As can be seen from Fig. 7, each titration of SC5A into the sample cell gave an apparent reaction heat, caused by the formation of inclusion complex between SC5A and PFM. The reaction heat decreases after each injection of SC5A because fewer and fewer guest molecules are available to form inclusion complexes. A control experiment was carried out in each run to determine the dilution heat by injecting a host aqueous solution into a pure aqueous solution containing no guest molecules. The dilution heat determined in these control experiments was subtracted from the apparent reaction heat

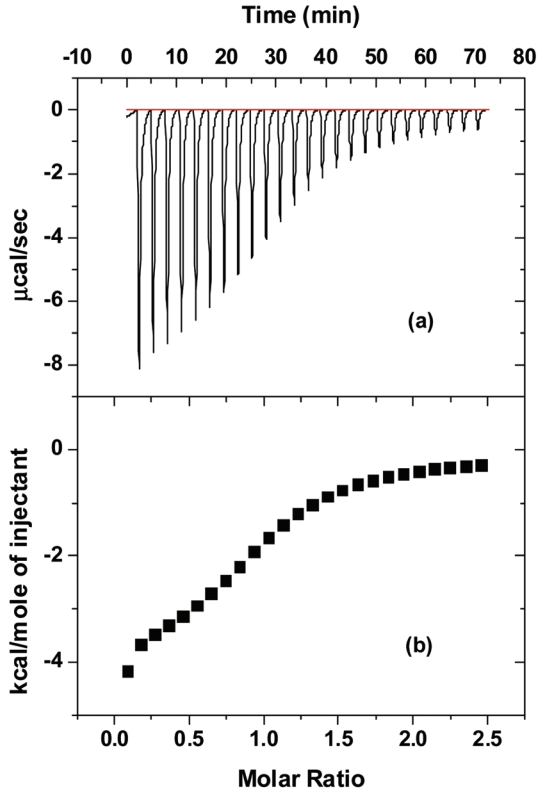

Fig. 7 Microcalorimetric titration of SC5A with PFM in aqueous solution (pH 2.0) at 298.15 K. (a) Raw data for sequential 25 injections (10 μL per injection) of SC5A solution (7.53 mM) injecting into PFM solution (0.58 mM). (b) Apparent reaction heat obtained from the integration of calorimetric traces.

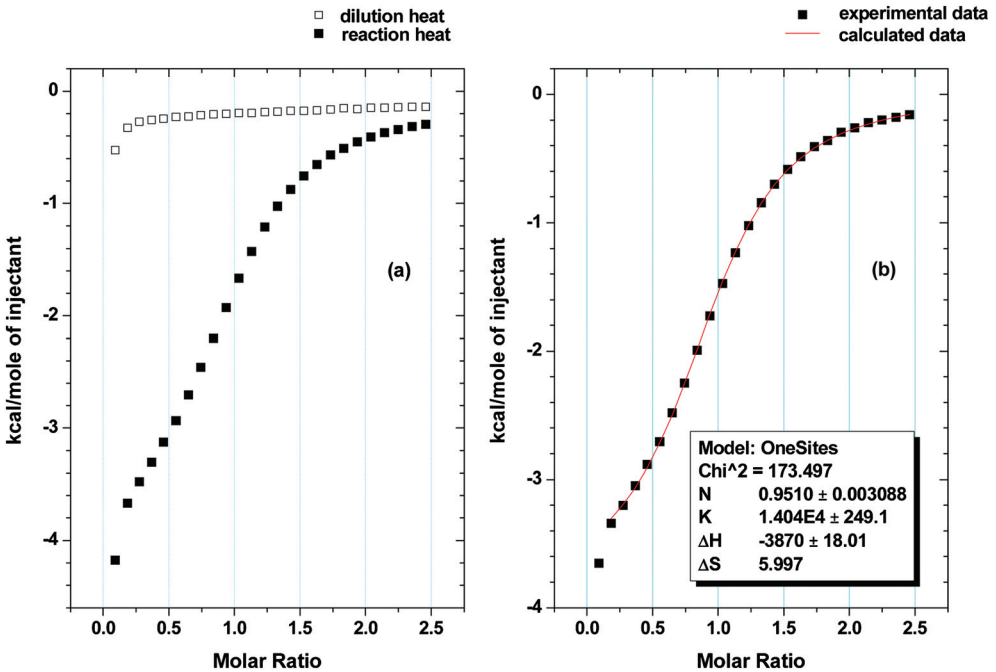

Fig. 8 (a) Heat effects of the dilution and of the complexation reaction of SC5A with PFM at pH 2.0 for each injection during titration microcalorimetric experiment. (b) "Net" heat effects of complexation of SC5A with PFM for each injection, obtained by subtracting the dilution heat from the reaction heat, which was fitted by computer simulation using the "one set of binding sites" model.

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measured in the titration experiments to give the net reaction heat.

The net reaction heat in each run was analyzed by using the "one set of binding sites" model (ORIGIN software, Microcal Inc.) to simultaneously compute the binding stoichiometry (N), complex stability constant (K_S), standard molar reaction enthalpy ($\Delta H°$) and standard deviation from the titration curve. Generally, the first point of the titration curve was disregarded, as some liquid mixing near the tip of the injection needle is known to occur at the beginning of each ITC run. Knowledge of the complex stability constant (K_S) and molar reaction enthalpy ($\Delta H°$) enabled calculation of the standard free energy ($\Delta G°$) and entropy changes ($\Delta S°$) according to

$$\Delta G° = -RT\ \ln K_S = \Delta H° - T\Delta S°$$

where R is the gas constant and T is the absolute temperature.

A typical curve fitting result for the complexation of SC5A with PFM at pH 2.0 was shown in Fig. 8. To check the accuracy of the observed thermodynamic parameters, two independent titration experiments were carried out to afford self-consistent thermodynamic parameters, and their average values were listed in Table 1 and 2.

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