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REVIEW ARTICLE

Selective binding behaviors of p-sulfonatocalixarenes in aqueous solution

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Abstract The complex structures, binding abilities, molecular selectivities, and thermodynamic origin of p-sulfonatocalixarenes upon complexation with kinds of guests are outlined in this review article, including inorganic cations, organic ammonium cations, pyridiniums and viologens, neutral organic molecules, dye molecules, and others. Calorimetric and spectroscopic investigations afford the complex stability constants, thermodynamic parameters and binding manners of the inclusion complexation of p-sulfonatocalixarenes with guest molecules. The p-stacking, hydrophobic and charge interactions are the main driving-forces during the course of the host–guest inclusion complexation. The molecular binding abilities and selectivities are in uenced by not only the frameworks of calixarene cavities, structures of guest molecules, and their binding manners but also the conditions of solutions (mainly pH), which are discussed from the correlation between the structural features and molecular-recognition abilities. Moreover, the further applications and potentials of p-sulfonatocalixarenes are brie y described.

Keywords p-Sulfonatocalixarenes · Complexation · Structures · Thermodynamics

Introduction

Calixarenes represent a particularly signi cant class of the host molecules in supramolecular chemistry, which are described as ‘macrocycles with (almost) unlimited possibilities’ for their facile modi cation [1]. Among these various calixarene derivatives, the chemistry of p-sulfonatocalixarenes are much more fascinating for their water-solubility as most biological progresses occur in aqueous solution [2]. Scheme 1 shows the structures of ve familiar p-sulfonatocalixarenes: p-sulfonatocalix[4]arene (C4AS), p-sulfonatothiacalix[4]arene (TC4AS), p-sulfonatocalix[5]arene (C5AS), p-sulfonatocalix[6]arene (C6AS), p-sulfonatocalix[8]arene (C8AS). p-Sulfonatocalixarenes possess the three-dimensional, exible, rich cavities, and also can provide the additional anchoring points of sulfonate groups, which endows them versatile inclusion/complexation properties for kinds of guest molecules. During the last two decades, the ionic/molecular recognition based on p-sulfonatocalixarenes has been widely investigated by our group and others. Furthermore, p-sulfonatocalixarenes are demonstrated to promise biological, pharmaceutical, analytical and crystal-engineering applications owing to their perfect pre-organized structures and special binding characteristics, which has been reviewed by Atwood, Raston and Coleman in recent years, respectively [3].

In this review, we wish to summarize the related investigations concerned on the binding abilities and structures of p-sulfonatocalixarenes and their thermodynamic origins, which will be discussed from the aspect of the types of guest molecules: (1) inorganic cations; (2) organic ammonium cations; (3) pyridiniums and viologens; (4) neutral organic molecules; (5) dye molecules; (6) others. Finally, some typical applications of p-sulfonatocalixarenes are described.

Synthesis of p-sulfonatocalixarenes and their derivatives

p-Sulfonatocalixarenes are prepared simply by the direct reaction of (p-tert-Butyl- or H-)calixarenes with conc.

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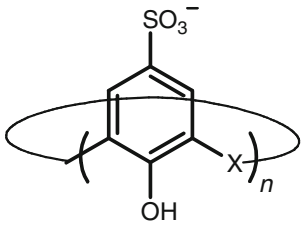


C4AS: X = CH_2, *n* = 4
TC4AS: X = S, *n* = 4
C5AS: X = CH_2, *n* = 5
C6AS: X = CH_2, *n* = 6
C8AS: X = CH_2, *n* = 8

Scheme 1 Structures of five familiar *p*-sulfonatocalixarenes

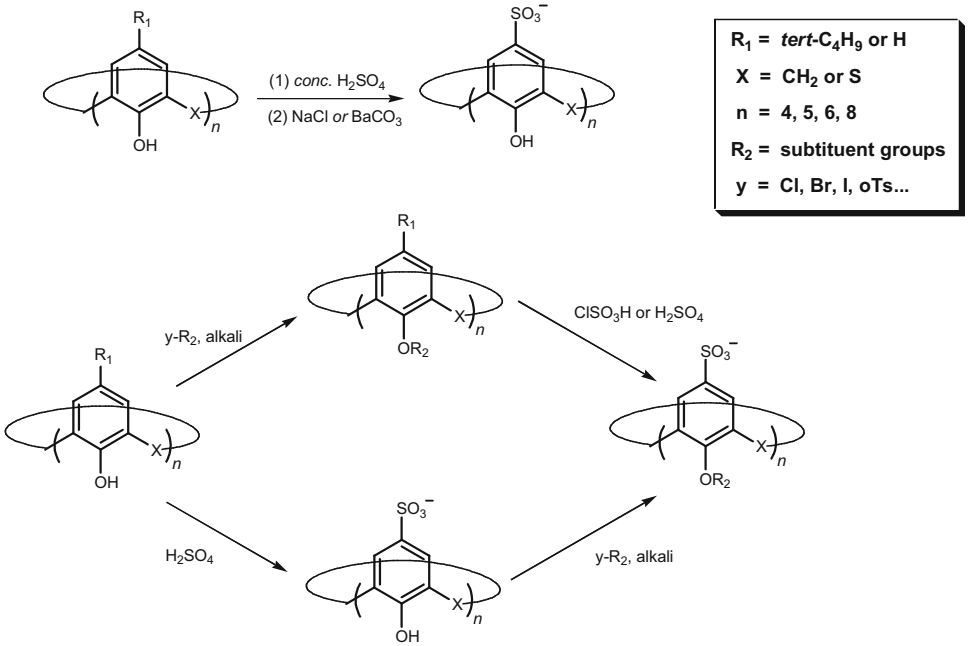
H_2SO_4, followed by treating with inorganic salts [4–6]. Moreover, to further expand the binding properties of *p*-sulfonatocalixarenes, a lot of derivatives have been synthesized by modifying the lower-rim. Generally, there are two routes to obtain *p*-sulfonatocalixarene derivatives as shown in Fig. 1. Shinkai et al. reported the synthesis of various *p*-sulfonatocalix[6]arene derivatives for the first time by the direct substitution of the lower-rim [7]. Reinaud and co-workers reported the synthesis of *p*-sulfonatocalix[6]arene derivatives using calix[6]arene modified at the lower-rim as material [8]. Silva and Coleman reported the synthesis of a series of mono-hydroxy functionalised *p*-sulfonatocalixarenes [9]. Arena et al. reported the synthesis of dicarboxylic acid derivative of *p*-sulfonatocalix[4]arene [10]. Raston and co-workers reported the synthesis of water-soluble *p*-sulfonatocalixarene derivatives with extended arms [11–13]. Moreover, *p*-sulfonatothiacalix[4]arene, as a new analogue of *p*-sulfonatocalixarene family, can be modified via oxidating its bridged S [14]. Some typical *p*-sulfonatocalixarene derivatives discussed in this review are shown in Scheme 2.

Binding behaviors and thermodynamics

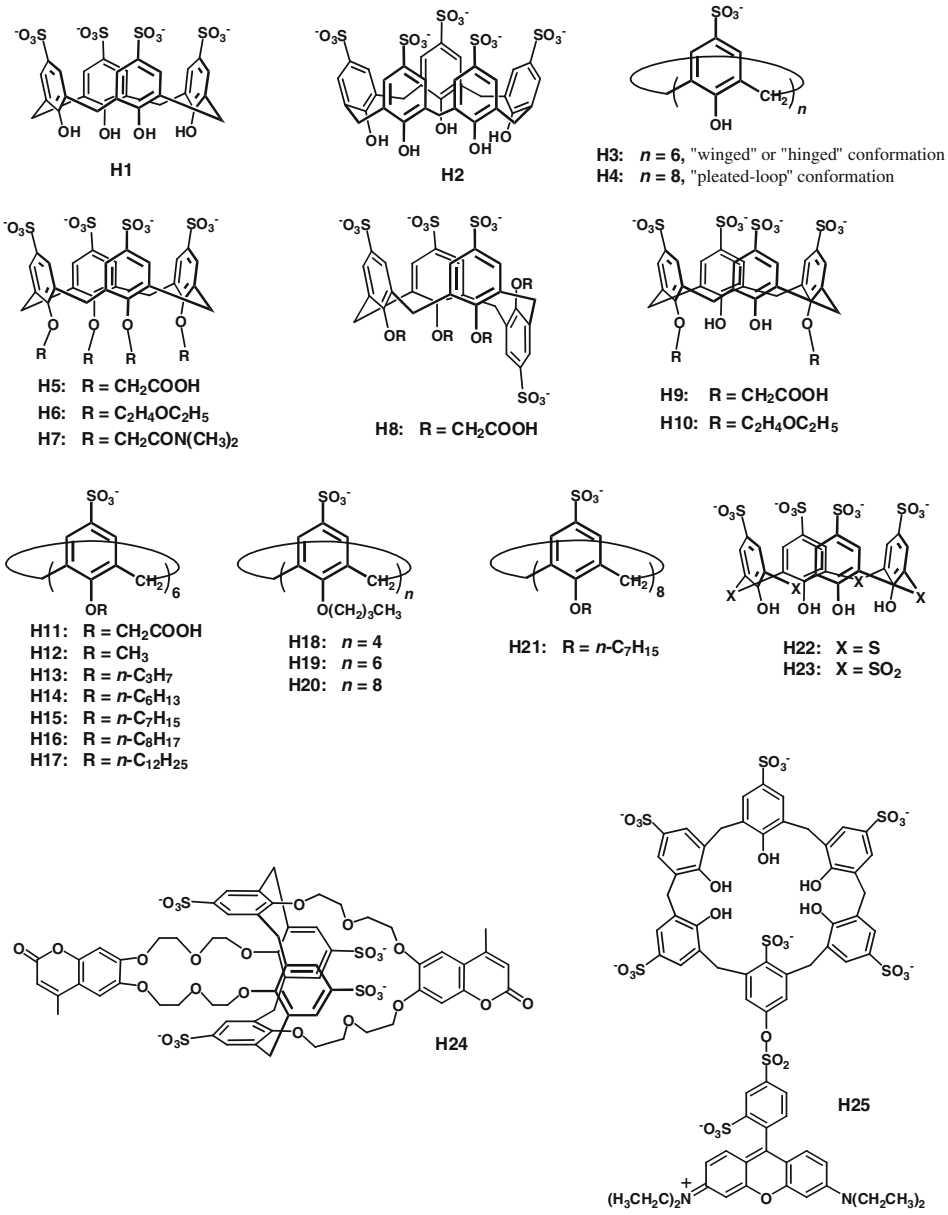
Binding with inorganic cations

The binding affinities and thermodynamics of H1 upon complexation with kinds of metal and ammonium ions (Na^+, K^+, Rb^+, Cs^+, Ag^+, Tl^+, NH_4^+, Ca^{2+}, Mg^{2+}, La^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Dy^{3+}, Yb^{3+}) were investigated utilizing ITC (isothermal titration calorimetry) method by Bonal and Morel-Desrosiers et al. [15, 16]. The obtained data of complex stability constants (K_S), enthalpy and entropy changes (ΔH and $T\Delta S$) are listed in Table 1. H1 forms 1:1 binding stoichiometry with the determined cations except for Na^+ and Ag^+ (no significant heat effect detected), in which H1 shows much weak binding abilities for monovalent cations and moderate strong binding abilities for divalent and trivalent cations. Thermodynamically, the complexation of H1 with monovalent cations is enthalpy-driven accompanied with negative or small positive entropy changes, whereas the complexation of H1 with divalent and trivalent cations is absolutely entropy-driven accompanied with unfavorable enthalpy changes. It indicates that the binding geometries between monovalent and multivalent cations are distinct from each other. The monovalent metal ions are included into the cavity of H1 due to the cation–π interactions. Herein, it should be mentioned that the Tl^+–π interaction is particularly favorable due to the cation polarizability, presenting much better K_S value up to 460 M^{-1} than other monovalent ions. The divalent and trivalent metal ions are hydrated to more extent than the monovalent ones, and then are not included into the cavity of H1. In fact, the relatively stable

Fig. 1 The synthetic routes of *p*-sulfonatocalixarenes and their derivatives



Scheme 2 Structures of *p*-sulfonatocalixarenes and derivatives employed in this review



association of H1 with multivalent metal ions occurs outside the cavity and it is a typically outer-sphere progress involving strong electrostatic interactions, in which the positive enthalpy and entropy changes are essentially originated from the partial desolvation of ^{n+}M and SO_3^- upon interaction and from the consequent release of water molecules. Moreover, the affinities for alkaline-earth ions are almost one order of magnitude lower than those for lanthanoid(III) ions, mainly owing to the less important desolvation of the divalent cations.

Furthermore, our group reported the complexation phenomena of a series of lanthanoid(III) ions (^{3+}La, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Tb^{3+}) with H5 and H22 and their thermodynamic origins [17]. All the guests and hosts can form stoichiometric 1:1 complexes. Resembling the case of H1, the complexation of H5 and H22 with lanthanoid(III) ions is also entropy-driven due to the extensive desolvation effect. As comparison with H1, H22 gives not only the lower complex stability constants for the increasing molecular exibility and decreasing electrostatic interactions but also the lower cations selectivity. The trivalent Nd^{3+} and Sm^{3+} could be best accommodated in the preorganized 3D cavity composed of four carboxyl groups upon complexation with lanthanoid ions, which could be explained for the reason that the preorganized structure of sulfonatocalixarene plays an important role in multi-site interaction with the lanthanoid(III) ions. All of the three water-soluble calixarenes give the lowest complexes stability constants for Eu^{3+} among lanthanoids investigated with much larger positive enthalpy and entropy changes at

Table 1 Complex stability constants (K_S/M^{-1}), standard enthalpy (ΔH /(kJ mol^{-1})), and entropy changes ($T\Delta S$ /(kJ mol^{-1})) for intermolecular complexation of inorganic cations with *p*-sulfonatocalixarenes in pH = 2 acidic aqueous solution at 298.15 K

Hosts	Cations	$\lg K_S$	ΔH	$T\Delta S$	Refs.
H1	Na^+	–	–	–	[16]
	K^+	0.46	−12.3	−9.7	
	Rb^+	0.77	−10.3	−5.9	
	Cs^+	1.2	−10.9	−4.3	
	Tl^+	2.7	−14.0	1.2	
	Ag^+	–	–	–	
	NH_4^+	0.84	−3.7	1.1	
	Mg^{2+}	3.30	4.7	23.5	[15]
	Ca^{2+}	3.32	3.0	22	
	La^{3+}	4.23	9.2	33.3	
	Nd^{3+}	4.08	9.5	32.8	
	Sm^{3+}	3.82	10.4	32.2	
	Eu^{3+}	3.83	12.5	34.4	
	Gd^{3+}	3.94	9.8	32.2	
	Dy^{3+}	3.88	10.1	32.3	
	Yb^{3+}	3.81	10.0	31.8	
H22	La^{3+}	3.45	7.2	26.8	[17]
	Ce^{3+}	3.41	7.0	26.5	
	Pr^{3+}	3.42	6.9	26.5	
	Nd^{3+}	3.40	6.8	26.2	
	Sm^{3+}	3.37	7.2	26.4	
	Eu^{3+}	3.26	7.5	26.0	
	Gd^{3+}	3.30	9.0	26.6	
	Tb^{3+}	3.33	7.7	26.7	
H5	La^{3+}	3.73	5.1	26.5	
	Ce^{3+}	3.82	5.1	26.9	
	Pr^{3+}	3.97	4.5	27.2	
	Nd^{3+}	4.09	4.0	27.4	
	Sm^{3+}	4.08	3.9	27.2	
	Eu^{3+}	3.51	7.3	27.4	
	Gd^{3+}	3.86	5.5	27.5	
	Tb^{3+}	3.63	6.8	27.7	

–, No significant heat effect

the same time, suggesting that this process is favored predominantly by the entropy gain, which is however canceled by similarly large unfavorable enthalpy changes.

Malfreyt and co-workers have also studied the complexes of H1 with rare-earth metal ions in aqueous solution using the method of molecular dynamics simulations [18]. The results obtained show that an outer-sphere complex is formed with the lanthanide cations located outside the cavity of H1, which preserves the conformational flexibility of H1 in the complex.

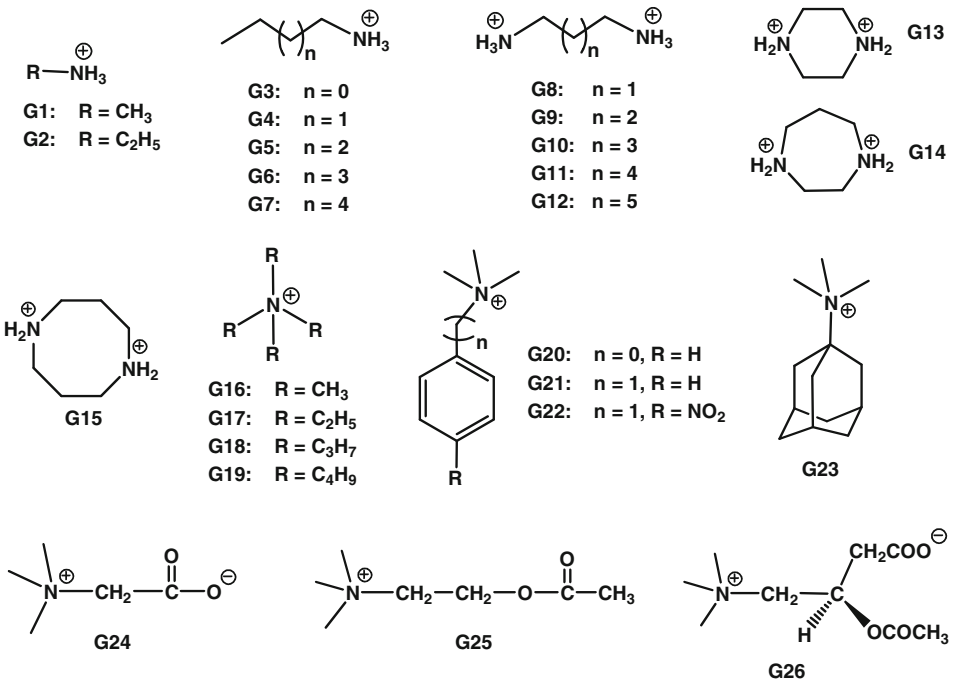
Yoshida and co-workers studied the interactions of H4 with divalent metal ions (Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and UO_2^{2+}) in aqueous solution by the method of pH titration [19]. The results obtained show that Cu^{2+} cannot form complex with H4. All the other divalent metal ions except for UO_2^{2+} could form weak complexes with H4 with 1:1 stoichiometry. In contrast, H4 could form a relatively stable 1:2 complex with UO_2^{2+}. All the conclusions indicate that H4 is a highly selective host compound for UO_2^{2+} among a series of divalent metal ions. The binding of UO_2^{2+} by the other *p*-sulfonatocalixarenes has also been reported by Shinkai et al. that both H2 and H3 can form stoichiometric 1:1 complexes with UO_2^{2+} [20]. Yoshida et al. reported that H1 could form a stoichiometric 2:1 complex with this UO_2^{2+} ion [21]. All the results indicate that the stoichiometry for the complex of sulfonatocalixarene with UO_2^{2+} is determined by the size of the host cavity.

Binding with organic ammonium cations

Possessing the *p*-rich cavities and the additional anchoring points offered by sulfonate groups, *p*-sulfonatocalixarenes display especially strong binding abilities and high molecular selectivity for given organic cations, which origins mainly from the cooperation of *p*-stacking and charge interactions. In this context, organic ammonium cations are one class of typical guests, including primary ammonium, secondary ammonium, and quaternary ammonium cations. Up to now, over 30 kinds of organic ammonium cations have been investigated upon complexation with *p*-sulfonatocalixarenes. Scheme 3 illustrates the selected 26 guests, and Table 2 lists their K_S values, enthalpy and entropy changes for intermolecular complexation with *p*-sulfonatocalixarenes, including H1, H2, H3, H4, H5 and H22. Among these *p*-sulfonatocalixarenes, H1 gains much more extensive investigations than the others, possibly owing to its ease of synthesis and steady conformation. The complexes of H1 with organic ammonium cations are entirely formed by enthalpy-driven accompanied with some either positive or negative entropy changes.

Stödeman and co-workers studied the interactions of alkylammonium ions (G3–G7) and α,ω-alkyl diammonium ions (G8–G12) with H1 in aqueous solution of pH 7.1 at 288.15, 298.15 and 308.15 K using ITC experiments [22, 23]. Bonal et al. further completed the investigations of the series of alkylammonium cations, and studied the interactions of H1 with methylammonium and ethylammonium cations (G1 and G2) in pH 2 solution [15]. Although the pH values are different from each other, the positively charged alkylammonium cations are located nearby the negatively charged sulfonate groups of H1, and the phenolic hydroxyls do not play a major role in the association progress. Therefore, the binding geometries between pH

Scheme 3 Structures of organic ammonium guests G1–G26



7.1 and pH 2 should be the same. For the present complexation cases of alkylammonium ions, the dominant enthalpy changes are mainly contributed by the van der Waals interactions associated with the inclusion of the alkyl chains, and the favorable (or small unfavorable) entropy changes originate from the major positive contribution of desolvation effect as well as the minor negative contribution of loss of conformational freedom. H1 forms more stable of one order of magnitude complex with G2 than G1, which is accompanied with more negative enthalpy change governed by the inclusion of the alkyl group within the cavity. For longer-chain species (G5–G7), the K_S values slowly decrease upon increasing the alkyl chain length, in which the enthalpy changes level off while the entropy changes become more and more unfavorable. This possibly results from that the augmentation of alkyl chain length leads to a more important loss of degrees of freedom. In addition, it should be mentioned that the complexation between α,ω-alkyl diammonium ions (G8–G12) and H1 is more complex than as described by 1:1, 1:2 or 2:1 models because of the bifunctionality of the diammonium ions.

Recently, the ITC experiments were performed in pH both 2.0 and 7.2 phosphate buffer solutions by our group to obtain the K_S values and thermodynamic parameters for the inclusion complexation of H1 and H22 with three diazacycloalkane guests, including piperazine (G13), homopiperazine (G14) and 1,5-diazacyclooctane (G15) [24]. It is found that the complexation of H1 and H22 with G13–G15 is well in accordance with the 1:1 binding stoichiometry, which is enthalpy-stabilized. Size–t relationship and pH value are two signi cant factors affecting the binding abilities of H1 and H22. Except for the H1 G13 complex, all the other complexes are more stable in an acidic buffer (pH 2.0) than in a neutral one (pH 7.2) due to one more protonation of the guests. Both host selectivity and guest selectivity are observed because of size–t relationship. H1 forms more stable complexes with guest molecules than H22 in either an acidic or a neutral buffer solution with more negative enthalpy changes because of its smaller cavity that ts the size of diazacycloalkane guests better.

Shinkai et al. rstly investigated the interactions of quaternary ammonium cations G20 and G23 with H1, H3 and H4 by the method of NMR spectroscopy [27, 32]. They found that H1 and H3 formed stoichiometric 1:1 complexes with G20 and G23, whereas H4 formed stoichiometric 1:2 complexes with them unexpectedly. The K_1 value is almost equal to the K_2 value. The formation of the stoichiometric 1:2 complex is primarily attributed to the large and exible ring of H4. The driving force for the complexation of H1 with G20 and G23 is electrostatic interaction, giving negative enthalpy changes due to its rigid and open conformation and strong anionic electrostatic eld. However, that for the case of H4 is hydrophobic interactions, giving positive entropy changes. The binding abilities of H3 with the guests are weaker than H1 and H4 because of its intermediary case between H1 and H4 affording neither electrostatic interactions nor hydrophobic interactions ef ciently. The binding abilities of G23 with p-sulfonatocalixarenes are stronger than G20 due to the increasing entropy changes arising from the

Table 2 Complex stability constants (K_S/M^{-1}), standard enthalpy (ΔH /(kJ mol^{-1})), and entropy changes ($T\Delta S$ /(kJ mol^{-1})) for intermolecular complexation of organic ammonium cations with sulfonatocalixarenes in aqueous solution at 298.15 K

Hosts	Cations	pH	$\lg K_S$	ΔH	$T\Delta S$	Methods	Refs.
H1	G1	2	2.65	−11.5	3.6	ITC	[15]
	G2	2	3.58	−16.5	3.9	ITC	[15]
	G3	7.1	4.12	−16.89	6.61	ITC	[22]
	G4	7.1	4.01	−17.94	4.94	ITC	[22]
	G5	7.1	3.81	−20.24	1.48	ITC	[22]
	G6	7.1	3.60	−20.42	0.15	ITC	[22]
	G7	7.1	3.39	−20.86	−1.51	ITC	[22]
	G8	7.1	3.90	−10.2	12.1	ITC	[23]
	G9	7.1	4.52	−20.5	5.3	ITC	[23]
	G10	7.1	7.78	−25.8	1.5	ITC	[23]
	G11	7.1	4.65	−28.7	−2.1	ITC	[23]
	G12	7.1	7.57	−31.2	−5.1	ITC	[23]
	G13	7.2	3.02	−20.05	−2.85	ITC	[24]
		2.0	2.95	−9.13	7.71	ITC	[24]
	G14	7.2	3.93	−26.40	−3.96	ITC	[24]
		2.0	4.07	−20.32	2.91	ITC	[24]
	G15	7.2	4.02	−13.80	9.15	ITC	[24]
		2.0	4.14	−17.48	6.15	ITC	[24]
	G16	2	4.40	−26.0	−0.9	ITC	[15]
		7.3	4.9			NMR	[25]
	G17	2	4.67	−41.2	−14.5	ITC	[15]
	G18	2	4.47	−23.8	1.7	ITC	[15]
	G19	2	4.21	−21.6	2.4	ITC	[15]
	G20	7.3	4.6			NMR	[26]
		7.3	3.75	−25.9	−4.5	NMR	[27]
	G21	7.3	4.1			NMR	[28]
		7.2	4.08	−32.34	9.00	ITC	[29]
	G22	7.3	4.2			NMR	[28]
	G23	7.3	4.32	−23.9	0.8	NMR	[27]
	G24	7.2	2.62	−26.23	11.25	ITC	[29]
	G25	7.2	4.14	−30.12	6.49	ITC	[29]
	G26	7.2	2.81	−25.76	9.71	ITC	[29]
H22	G13	7.2	–	–	–	ITC	[24]
		2.0	–	–	–	ITC	[24]
	G14	7.2	2.39	−16.00	−2.80	ITC	[24]
		2.0	2.55	−8.47	6.10	ITC	[24]
	G15	7.2	–	–	–	ITC	[24]
		2.0	2.54	−7.95	6.55	ITC	[24]
	G21	7.2	3.27	−31.17	12.55	ITC	[29]
	G24	7.2	1.08	−10.29	4.02	ITC	[29]
	G25	7.2	2.73	−17.03	1.46	ITC	[29]
	G26	7.2	1.32	−15.15	7.53	ITC	[29]
H2	G16	7.3	3.6			NMR	[28]
	G20	7.3	4.2			NMR	[28]
	G21	7.3	4.0			NMR	[28]
	G22	7.3	5.1			NMR	[28]
H5	G16	7.0	3.5	−5.8	−0.9	NMR	[30]
	G20	7.0	3.3	−8.7	−4.2	NMR	[31]
	G21	7.0	3.2	−6.4	−2.0	NMR	[31]
	G22	7.0	3.4	−6.4	−1.8	NMR	[31]
H3	G20	7.3	2.74	−1.0	14.6	NMR	[27]
	G23	7.3	3.0	0.63	16.6	NMR	[27]
	G21	7.2	3.64	−34.98	14.23	ITC	[29]
	G24	7.2	2.42	−31.71	17.87	ITC	[29]
	G25	7.2	3.73	−35.06	13.81	ITC	[29]
	G26	7.2	2.75	−31.21	15.48	ITC	[29]
H4	G20	7.3	3.72[a]	0.0	21.2	NMR	[27]
			3.66[b]	0.0	20.8	NMR	[27]
	G23	7.3	4.28[a]	0.0	24.5	NMR	[27]
			4.23[b]	0.0	24.1	NMR	[27]

–, No signi cant heat effect

[a] $\lg K_{S1}$

[b] $\lg K_{S2}$

more hydrophobic property of the adamantly group in G20 is bound with H1 and H4 from either the aromatic moiety or the ammonium moiety without regioselectivity, however, it is bound with H3 from ammonium moiety selectively.

Arena et al. reported that G20 was included into the conformationally rigid cavity of H5 or H9 at neutral pH from the aromatic moiety selectively and the preorganization of host's cavity played an important role in determining the selective inclusion of the guest, regardless of the pH [10, 31]. They also investigated the interactions of some other hosts blocked in the cone conformation (H6, H7 and H10) and the partial-cone H8 with G16 and G20 at neutral pH to compare with the results concluded above [30]. The obtained data show that all the three hosts blocked in the cone conformation bind the aromatic portion of G20 selectively like H5 and H9. In contrast, the partial-cone H8 binds either the aromatic moiety or the ammonium moiety of G20 without regioselectivity like the conformationally mobile H1. The complex stabilities of H7 G20 and H10 G20 are comparable with H5 G20 and H9 G20, but are lower by one order of magnitude than H6 G20 as the result of the conformational and steric effects. Similarly, G16 is bond with H1, H5, H7–H10 but not with H6. H5 and H7 show much stronger binding abilities towards G16 than the difunctionalized H9 and H10. The conformationally mobile host H1 without binding regioselectivity in the binding of G20 affords the strongest binding abilities towards both G16 and G20 through adapting its cavity to the size of the guest, which implies that induced t recognition is often more ef cient than complexation by more pre-organized hosts. The

complexation of G21 and G22 with H5 at neutral pH was also investigated utilizing NMR spectroscopy and calorimetry by the same group [31], which showed that G22 was included into the host's cavity from aliphatic group selectively, whereas the host recognized either the aromatic moiety or the aliphatic group of G21 without regioselectivity. Thermodynamically, the interactions of the two guests with H5 are absolutely enthalpy-driven.

As comparison with H1, the complexation of H2 with quaternary ammonium guests (G16, G20, G21 and G22) was further investigated at neutral pH [28]. The results show that the driving forces for the complexes H1 G16 and H2 G16 are the same, which is the synergy of electrostatic and C–H p interactions. The complex stability of H2 G16 is weaker than H1 G16 due to its wider cavity. Similarly, the binding abilities of H1 for G20 and G21 are also much stronger than H2. However, the guest selectivity is different: the binding order is G16 > G20 > G21 for H1, whereas for H2, G20 and G21 are included more efficiently than G16. The reason for this phenomenon may be the different inclusion geometries between H1 and H2. As mentioned above, G20 [27] and G21 are included into the cavity of H1 without regioselectivity. Differently, H2 with the wider cavity is able to accommodate simultaneously both the charged group and the aromatic moiety of ditopic G20 and G21. H1 can only contribute two host–guest interactions (either p p and electrostatic or C–H p and electrostatic interactions) synchronously to capture G20 and G21, whereas H2 provides a synergy of three interactions (p p, C–H p and electrostatic interactions). For G22, H2 can also include both the charged group and the aromatic moiety into the cavity via three non-covalent interactions, while H1 can only include the charged group. Moreover, G22 with the electron-withdrawing nitro group in the para-position of the aromatic ring is included into the cavity of H2 more stably than G20 and G21 due to the more efficient p p interaction. In contrast, the binding stability of H1 with G22 is comparable with G21 because p p interaction is not involved in the complexation of H1 with G22 (Fig. 2).

Bonal et al. investigated the interactions of H1 with a series of quaternary ammonium cations (R_4N^+, G16–G19) possessing different chain-lengths in acidic solution at 298.15 K using microcalorimetry [15]. The results are consistent with the formation of 1:1 complexes. The complexation is enthalpy-driven, indicating that van der Waals interactions are the main driving forces with some contributions of hydrophobic interactions. The contribution of electrostatic interactions to the inclusion process is probably slight. The changes for thermodynamic parameters are nonlinear as chain-length increasing within the R_4N^+ series. The entropy changes for these processes are small except for G17. The reason for the big negative entropy change for the complexation of G17 with H1 may be the insertion of more than one ethyl group into the cavity resulting in an important loss of degrees of freedom. The entropy change for G16 is much smaller than G17 although it penetrates more deeply into cavity, indicating a less important loss of degrees of freedom. The small positive entropy changes for G18 and G19 imply the insertion of only one alkyl chain. Malfreyt and co-workers further studied the complexation of H1 with R_4N^+ cations and G1 in aqueous solution using the method of molecular dynamics simulations [18, 33], which also validated that quaternary ammonium cation was included into the cavity of H1. G16 penetrates into the cavity deeply, resulting in a rigid conformation. G1 is included into the cavity more deeply than G16, in which the methyl group is within the cavity whereas the three hydrogen atoms on N atom are located towards the upper rim of calixarene. In the case of G17, one of the alkyl chains is inside the cavity and the other two alkyl chains are close to the border of the cavity, giving a much more negative enthalpy change upon complexation with H1 than the other R_4N^+ cations. In the case of G18, only one alkyl chain is inside the cavity, while the others are outside the cavity, resulting in a certain exibility of H1 and a mobility of the cation. Upon complexation with these organic ammonium cations, the cavity of H1 becomes more open.

Our group have also studied the interactions of some quaternary ammonium cations (G21, and G24–G26) with H1, H3 and H22 in pH 7.2 phosphate buffer solutions at 298.15 K using calorimetric titration and NMR experiments [29]. All the guests and p-sulfonatocalixarenes employed could form stable stoichiometric 1:1 complexes. The NMR results show that G21 is included into the cavity of H22 from the aromatic moiety with regioselectivity, differing much from that of H1. The ITC results show that all the host–guest complexation is driven by favorable enthalpy changes that are attributed to p-stacking and van der Waals interactions, which is accompanied with negative entropy changes arising from the loss of conformational freedom. The host selectivity is similar, H1 > H3 > H22 for each guest. H1 affords the strongest binding abilities towards all the guests examined due to its

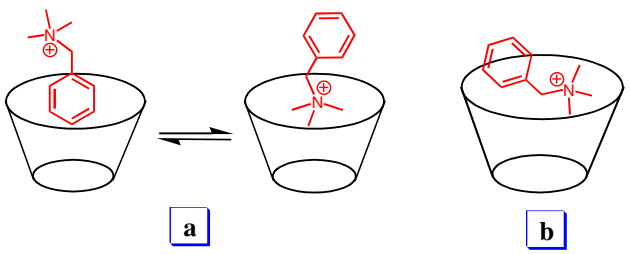


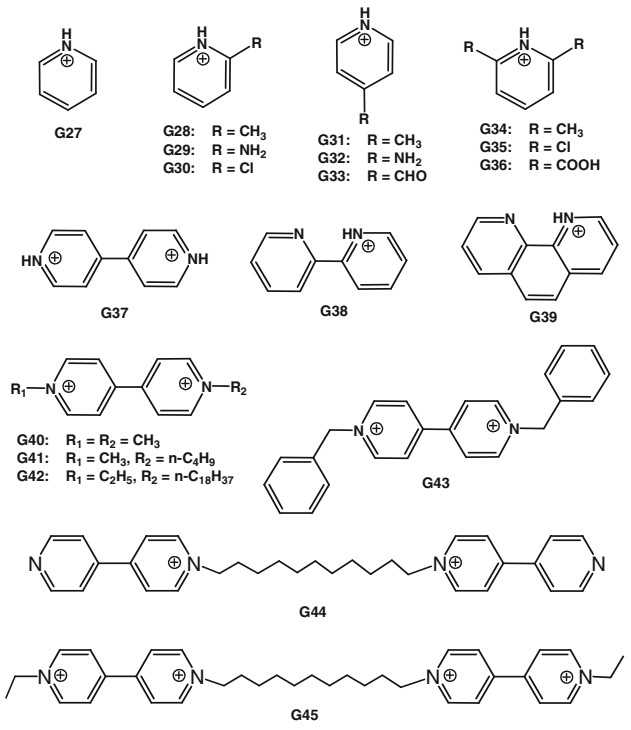
Fig. 2 Binding manners of G21 with H1 (a) and H2 (b)

smallest cavity and relatively high p-electron density that contribute to the good size–fit and strong C–H/p interactions between host and guest. All the hosts examined show much stronger binding abilities towards G21 and G25 than G24 and G26 that have electronegative carboxyl groups. The enthalpy changes for the complexation of both H1 and H22 with G21 are more negative than with the other guests due to the p–p interactions between host and the aromatic ring of G21. Jin investigated the inclusion phenomena of H1, H3 and H4 with fluorescent dansylcholine, affording a new fluorometric method for detection of the neurotransmitter acetylcholine [34].

Pyridiniums and viologens

As further pursuing the inclusion phenomena of p-sulfonatocalixarenes, their binding properties and thermodynamics with various pyridinium guests are systematically investigated utilizing ITC measurement by our group. Three smaller analogues, such as H1, H2 and H22, are selectively employed owing to their preferred cone shape. The guest molecules determined are illustrated in Scheme 4 (G27–G39).

The inclusion phenomena of H1 and H22 with pyridinium guest ions (G27–G36) were primarily investigated by the methods of NMR spectroscopy and ITC in pH 2.0 phosphate buffer solution (Table 2) [35]. These studies show that all the hosts and pyridinium guest ions form



Scheme 4 Structures of pyridinium and viologen guests G27–G45

stoichiometric 1:1 complexes. The ^{1}H NMR experiments show that pyridinium guest ions penetrate into the host's cavity from the para-position of N atom, which contributes to the significant electrostatic interactions between protonated N atom of guest and anionic sulfonate groups of host. The symmetry of guest as well as the induced-fit relationship between host and guest may be the main factors that control the binding modes for the complexes of host and guest. The ITC results show that all the host–guest inclusion complexation between p-sulfonatocalixarenes and pyridinium guest ions are driven by favorable enthalpy changes, accompanied with negative or slightly positive entropy changes. H1 affords stronger binding abilities towards pyridium guest ions than H22 because of its smaller cavity with relatively higher p-electron density that contributes to more favorable enthalpy changes. On the other hand, p-sulfonatocalixarenes afford stronger binding abilities towards two-substituted pyridiniums (G28 and G29) than four-substituted analogues (G31 and G32). Moreover, the binding abilities of p-sulfonatocalixarenes become stronger and stronger accompanied with the increasing number of methyl groups of guests. p-Sulfonatocalixarenes give significantly high binding abilities towards the methylated pyridinium guest ions due to their additional C–H p interactions.

We further studied the interactions of H1, H2 and H22 with pyridine and their methylated derivatives (G27, G28, G31 and G34) at different pH values (2.0 and 7.2) (Table 3) [36]. The NMR studies show that the conformation of H1 becomes rigid, while that of H2 remains flexible upon complexation with guests. The binding modes between H1 and H2 are similar except for the case of G31. That is, G31 penetrates into the cavity of H1 in the perpendicular orientation, while penetrates into the cavity of H2 in the acclivitous orientation. This is mainly attributed to the wider cavity of H2. The ITC results show that all of the host–guest inclusion complexation between p-sulfonatocalixarenes and guest pyridines are driven by favorable enthalpy changes, accompanied with negative entropy changes in both pH 2.0 and pH 7.2 conditions. p-Stacking, especially C–H p, and van der Waals interactions play an important role in the inclusion complexation, contributing to the dominant enthalpy changes. The enthalpy changes at pH 7.2 are somewhat higher than those at pH 2.0 because p-sulfonatocalixarenes possess higher p-electron density at pH 7.2 than pH 2.0. However, the entropy changes at pH 7.2 are remarkably more unfavorable than those at pH 2.0 because of the more extensive desolvation effects between protonated pyridinium guests and p-sulfonatocalixarenes at pH 2.0. As a total result, p-sulfonatocalixarenes afford stronger binding abilities towards pyridinium guests at pH 2.0 than towards pyridine guests at pH 7.2. Nevertheless, p-sulfonatocalixarenes present higher molecular selectivity

Table 3 Complex stability constants (K_S/M^{-1}), standard enthalpy (ΔH /(kJ mol^{-1})), and entropy changes ($T\Delta S$ /(kJ mol^{-1})) for intermolecular complexation of pyridiniums and viologens with *p*-sulfonatocalixarenes in aqueous solution by ITC at 298.15 K

Hosts	Cations	pH	$\lg K_S$	ΔH	$T\Delta S$	Refs.
H1	G27	2.0	3.92	−29.71	−7.34	[35]
		7.2	2.48	−41.1	−26.9	[36]
	G28	2.0	4.12	−34.70	−11.17	[35]
		7.2	3.13	−45.1	−27.2	[36]
	G29	2.0	3.72	−30.97	−9.73	[35]
	G30	2.0	3.23	−33.71	−15.27	[35]
	G31	2.0	3.65	−28.90	−8.08	[35]
		7.2	2.72	−41.2	−25.7	[36]
	G32	2.0	2.93	−22.99	−6.25	[35]
	G33	2.0	1.86	−26.47	−15.85	[35]
	G34	2.0	4.38	−38.57	−13.56	[35]
		7.2	3.83	−47.7	−25.8	[36]
	G35	2.0	2.54	−33.50	−19.03	[35]
	G36	2.0	1.83	−27.97	−17.50	[35]
	G37	2.0	3.07	−24.5	−7.0	[38]
		7.2	1.64	−8.3	1.1	[38]
	G38	2.0	4.01	−36.7	−13.8	[38]
		7.2	1.92	−37.8	−26.8	[38]
	G39	2.0	4.43	−44.8	−19.5	[38]
		7.2	2.44	−46.7	−32.8	[38]
	G40	2.0	4.49	−28.18	−2.53	[49]
		7.2	4.97	−31.98	−3.62	[49]
		12.0	4.97	−32.83	−4.46	[49]
H22	G27	2.0	2.65	−19.95	−4.83	[35]
		7.2	1.74	−30.5	−20.6	[36]
	G28	2.0	3.06	−28.22	−10.74	[35]
		7.2	2.32	−40.5	−27.3	[36]
	G29	2.0	2.72	−22.56	−7.05	[35]
	G30	2.0	2.15	−26.56	−14.27	[35]
	G31	2.0	2.78	−17.62	−1.73	[35]
		7.2	2.14	−37.6	−25.4	[36]
	G32	2.0	2.47	−6.98	7.33	[35]
	G33	2.0	–	–	–	[35]
	G34	2.0	3.48	−28.60	−8.71	[35]
		7.2	3.18	−43.6	−25.4	[36]
	G35	2.0	2.37	−12.02	1.48	[35]
	G36	2.0	1.83	−12.52	−2.24	[35]
	G37	2.0	2.72	−18.0	−2.5	[38]
		7.2	1.69	−16.7	−7.1	[38]
	G38	2.0	3.12	−27.5	−9.7	[38]
		7.2	1.76	−26.5	−16.5	[38]
	G39	2.0	3.70	−36.6	−15.5	[38]
		7.2	2.45	−41.9	−27.9	[38]
	G43	7.2	4.1[a]	−34.6	−11.2	[48]
			2.9[b]	−21.1	−4.2	
H2	G27	2.0	2.48	−16.1	−2.0	[36]
		7.2	1.86	−23.3	−12.7	[36]
	G28	2.0	2.75	−18.5	−2.8	[36]
		7.2	2.64	−38.9	−23.9	[36]
	G31	2.0	2.60	−16.5	−1.7	[36]
		7.2	2.43	−34.2	−20.3	[36]
	G34	2.0	2.99	−22.2	−5.1	[36]
		7.2	3.46	−38.2	−18.4	[36]
	G37	2.0	3.31	−30.0	−11.1	[38]
	G38	2.0	3.09	−28.4	−10.8	[38]
	G39	2.0	3.36	−38.8	−19.7	[38]
	G40	2.0	3.74	−20.58	0.79	[49]
		7.2	5.40	−31.52	−0.67	[49]
		12.0	5.53	−33.11	−1.53	[49]

–, No signi cant heat effect

[a] $\lg K_{S1}$

[b] $\lg K_{S2}$

at pH 7.2 than pH 2.0 due to the strengthened C–H p interactions. H22 affords the stronger binding abilities at pH 2.0 than H2 due to its smaller cavity that contributes to a better size– t relationship with pyridinium guests. However, at pH 7.2, the binding abilities are opposite, H2 > H22, resulting from that H2 affords the stronger p p and C–H p interactions with pyridine guests than H22.

The inclusion complexation of dipyridiniums (G37 and G38) and 1,10-phenanthrolinium (G39) with H1, H2 and H22 has also been studied at acidic and neutral conditions by our group (Table 3) [37–39]. Resembling the cases of pyridinium guests, *p*-sulfonatocalixarenes also form stoichiometric 1:1 complexes with dipyridiniums and phenanthrolinium. The host–guest binding modes were determined by the combination of NMR spectroscopy and X-ray crystallography. The 2D NMR studies show that G37, G38 and G39 are included into the cavity of H2 with the different patterns (Fig. 3a–c), i.e., accumbent for G37, acclivitous for G38 and G39, and the cone conformation of H2 is invariable before and after complexation with guests. To the contrary, G39 is included upright into the cavity of H1 with the conformation rigidi ed (Fig. 3d), while G37 is located outside H1, and its cone shape is disrupted by G37 to assume the 1,3-alternate conformation in the solid-state [40]. The crystal structures show that the intrinsic cone shape of H22 is disrupted to the 1,2-alternate conformation upon complexation with G37, and H1 and H22 maintain their original cone conformations with slantways inclusion of G38 (Fig. 4). Moreover, the binding modes between

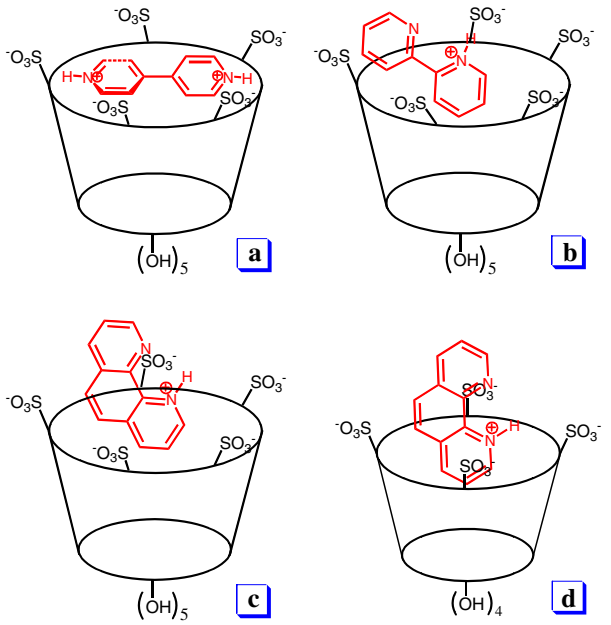


Fig. 3 Deduced binding modes of guests G37–G39 with H1 and H2

p-sulfonatocalixarenes and G39 are pH-dependent that G39 penetrates into the cavities of H2 and H22 in the vertical orientation at pH 1–2, while in the horizontal orientation in 1 M HCl solution, which are well identified by 2D NMR spectroscopy and X-ray crystallography. The cavity size of host molecules and the conjugation degree of guest molecules are the two most important factors to the formation of inclusion complexes, while electrostatic interaction does not play a crucial role in this process. For the complexation of the three hosts with G38 or G39, the K_S values obtained decrease with increasing cavity size. However, the binding abilities of the three hosts with G37 are much different, and the binding order is H2 > H1 > H22. The reason for this phenomenon is the different binding modes of these three host–guest inclusion complexes. The K_S values obtained for the complexation of the guests with H1 and H22 decline with decreasing conjugation degree of guest molecules, G39 > G38 > G37, which is owing to that larger conjugated π system affords the stronger π-stacking interactions with the host cavities. The order for the binding abilities of H2 with the three guests is different due to its unique binding mode with G37, G39 > G37 > G38. The ITC results at pH 7.2 show that the binding abilities of H1 and H22 with the three guests at pH 7.2 are much weaker than those at pH 2.0 due to the desolvation effect, which is similar to the cases of pyridinium guests. The binding abilities of H2 and H22 with G39 in 1 M DCl have been studied by the method of NMR, which shows that the K_S values of H2 and H22 with G39 in 1 M DCl are much less than those at pH 2.0 resulting from the protonation of sulfonate groups and the different binding mode.

Viologens are one class of important redox couples [44], widely used in many fields, such as herbicides [42], probes to study DNA and zeolites [43], subunits in constructing functional molecular assemblies/machines [45] and components of electrochromic display devices [45]. So the researches of complexation of viologens by p-sulfonatocalixarenes are promised to be quite meaningful. The interactions between some viologen guests (G40–G42) (Scheme 4) and p-sulfonatocalixarenes (H3, H17 and H19) were firstly studied with the methods of NMR spectroscopy and voltammetric techniques by Kaifer and co-workers [46]. It is found that H3 could form a stable complex with G40 in water solution. The formation of inclusion complexes of H19 G41 and H17 G42 was also confirmed by different methods. The structure of H19 G41 complex was inferred by the method of 2D NOESY NMR spectroscopy that G41 was included into the cavity of H19 with its butyl chain contacting the calixarene's six butyl chains. The same group further investigated the inclusion properties of H12 with dimeric viologen guests (G44 and G45) (Scheme

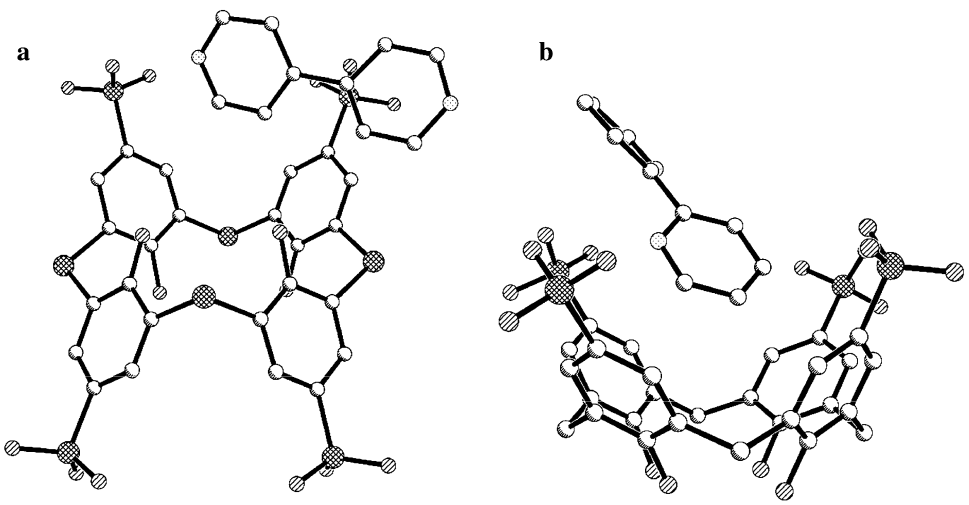


Fig. 4 The solid-state structures of H22 G37 (a) and H1 G38 (b)

4) [47]. H12 affords strong binding abilities towards the two guests in 0.2 M NaCl (aq). Electrostatic interaction is the main driving force for the complexation. The binding modes of the two guests by H12 are similar that the host cavity is threaded by the long guest with positive charges at two ends of the guest perfectly positioned to interact with the negative charges in each of the sides of H12 cavity. Therefore, H12 provides the similar binding a nity to the two guests possessing different positive charges.

Our group reported the binding mode and thermodynamics of H22 G43 complex in neutral conditions using ^{1}H NMR spectroscopy, ITC and single-crystal X-ray diffraction experiments (Table 3) [48]. H22 and G43 could form stoichiometric 1:2 complex and two G43 guests are attached to the upper and lower rim of H22 in sequence. G43 prefers to bind at the upper rim of H22 accompanied with a larger favorable enthalpy contribution due to hydrophobic, C–H p and p p interactions. The second binding constant is less than the rst one due to a less enthalpy contribution resulting from weak C–H p, C–H O and van der Waals interactions although the entropy loss in the second step is less than the rst step. Recently, we also investigated the binding behavior of H1 and H2 with G40 and its radical cation in different pH conditions (Table 3) [49]. Differing from the case of H22 G43, H1 and H2 form stoichiometric 1:1 complexes with G40. The ^{1}H NMR and 2D ROESY NMR experiments show that the binding modes of H1 and H2 with G40 are different from each other. G40 is immersed into the cavity of H1 in its axial orientation with the methyl group being included rstly while it lies at the upper-rim midsection of H2 in the latitudinal orientation (Fig. 5). It can be easily seen from the ITC results that H1 and H2 can form much more stable complexes with G40 than H3 that affords weak binding abilities towards G40 with alternative conformation [47]. The binding abilities of H1 and H2 with G40 become stronger when the pH value increases, which is absolutely driven by enthalpy term. The host selectivity for H1/H2 pairs is reversed with increasing pH value: H1 > H2 in acidic condition but H2 > H1 in neutral and basic condition. This phenomenon can be explained from two viewpoints: One is the p-electron density of the calixarene's cavity and the other is the different binding modes of the two hosts with G40. The effective inclusion of H1 or H2 with the radical cation of G40 was also con rmed by cyclic voltammetry. However, the binding a nities of H1 or H2 with the radical cation of G40 are obviously weaker than those with G40 due to the weaker p-electron acceptor and hydrogen-bonding donor abilities of its radical cation.

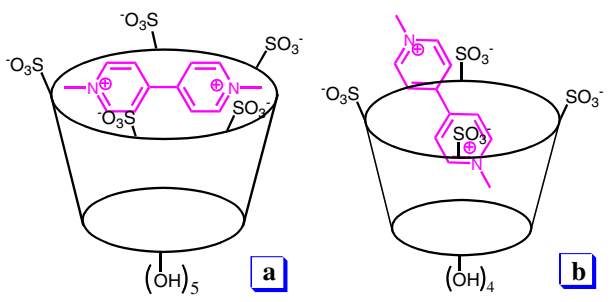
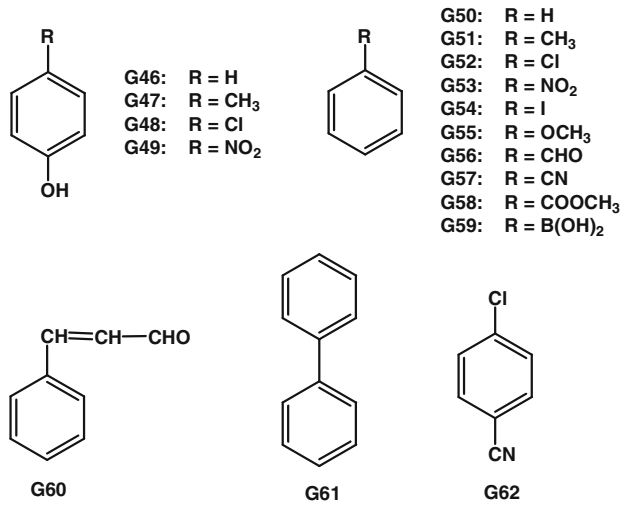


Fig. 5 Deduced binding manners of H2 (a) and H1 (b) with G40

Binding with neutral organic molecules

Sciotto et al. have studied the interactions between alcohols, ketones, nitriles and p-sulfonatocalixarenes (H1, H5, H6 and H10) by ^{1}H NMR spectroscopy [50, 51], which found that the apolar aliphatic portions of the guests were included into the host hydrophobic cavity with the terminal polar groups of the guests directed towards the polar sulphonate groups of the host and to the solvent. The two most important factors for the complexation of the investigated hosts and guests are conformational properties of the receptors and electrostatic effects. Methanol is not included at all by p-sulfonatocalixarenes for the possible reason that the inclusion of small methyl group inside the hydrophobic cavity would lead to a partial inclusion of polar OH group causing the polar hydroxyl group to be less exposed to polar solvent. Malfreyt and co-workers further studied the complexation of H1 with linear alcohols in water at 298.15 K using the method of molecular dynamics simulations [52]. The inferred binding mode is similar to that described by Sciotto et al. The OH group of ethanol and propanol can be totally inserted into the lipophilic cavity of H1 whereas it is only partially inserted for alcohols with longer alkyl chains, which results in the hydroxyl group of alcohol molecules being away from the upper rim of H1. The complexation of H1 with guests is mainly controlled by van der Waals interactions. Miyano and co-workers have studied the interactions of H22 with some water-miscible organic molecules utilizing the methods of salting-out and X-ray crystallography [53]. H22 prefers to include rather small alcohols for a series of alkyl alcohols except methanol. The binding manner of H22 with alcohols is similar to that of H1. Moreover, the linear alcohols are much more favorable to be included by H22 than the branched ones. Ketones are not favorable to be bond by H22 because of its nonlinear shape with no hydrogen donor. Such combination of molecular recognition and phase transition is promised to apply for the separation of water-miscible organic molecules from the aqueous solutions.

Kunsági-Máté et al. investigated the complexation of H3 with G46–G49 (Scheme 5) at pH 6.9 using PL, DSC and quantum-chemical methods [54]. These phenolic derivatives can enter into the cavity of H3, forming the



Scheme 5 Structures of neutral organic guests G46–G62

stoichiometric 1:1 complexes, in which p p interaction between the aromatic rings of host and guest is the main driving force for the inclusion complexation. The enthalpy changes for the complexation of phenolic derivatives with H3 is quite favorable, however, the complex stability is relatively low due to the highly negative entropy changes. The stabilities of the host–guest complexes increase accompanied with the enhancement of electron density on the guest's aromatic ring. This phenomenon can be explained by the enthalpy–entropy compensation effect although the enthalpy term becomes unfavorable during this process.

The interactions of aromatic substrates (G51, G54, G56, and G59–G62) (Scheme 5) with H1 and H3 were studied by Schatz and co-workers via ^{1}H NMR titration experiments and molecular modeling studies combined with ab initio NMR shift calculation at neutral aqueous solutions [55]. All the guests are included into the cavities of hosts, which is mainly driven by enthalpy term. In most cases, the ve aromatic protons are pointing inside and the functional group of guest is located outside the cavities of hosts due to hydrophobic and p p interactions. For G51, the binding mode of the complex is different and that is the methyl group is included into the cavity of the host, contributing to the favorable C–H p interactions. For G62, the Cl substituent of the guest prefers to enter into the cavity of the host than the CN substituent.

Miyano and co-workers comparatively studied the interactions of H1 and H22 with mono-substituted benzenes (G50–G53, G55 and G57–G58) (Scheme 5) using NMR spectroscopy in neutral aqueous solutions [56]. The results show that all the guests and hosts could form stoichiometric 1:1 complexes. Except the complexation of G51 by H1, all the other guests are included into the cavities of hosts from the aromatic moiety with regioselectivity. For the case of G51 with H1, either the aromatic or the methyl group could enter into the host cavity with no regioselectivity due to the smaller host cavity, which affords additional C–H p interactions. The inferred binding modes of the complexes are shown in Fig. 6. The inclusion complexes with electron-withdrawing substituent on the guest are much more stable than that with electron-donating substituent, suggesting that p interaction plays an important role in the complexation. H22, with lower electron density and larger cavity than H1, is more ef cient for the complexation of mono-substituted benzenes except for G51, suggesting that the size rather than the electron density of the host framework plays a more important role in determining the inclusion ability. For the case of G51,

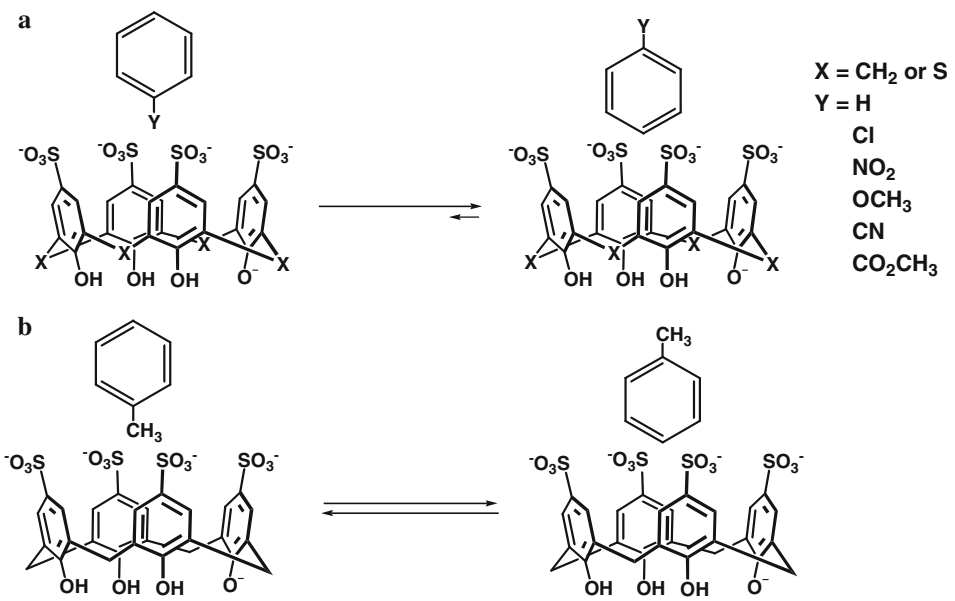


Fig. 6 Complexation modes of H1 and H22 towards mono-substituted benzenes a (except that of H1 towards G51 (b)

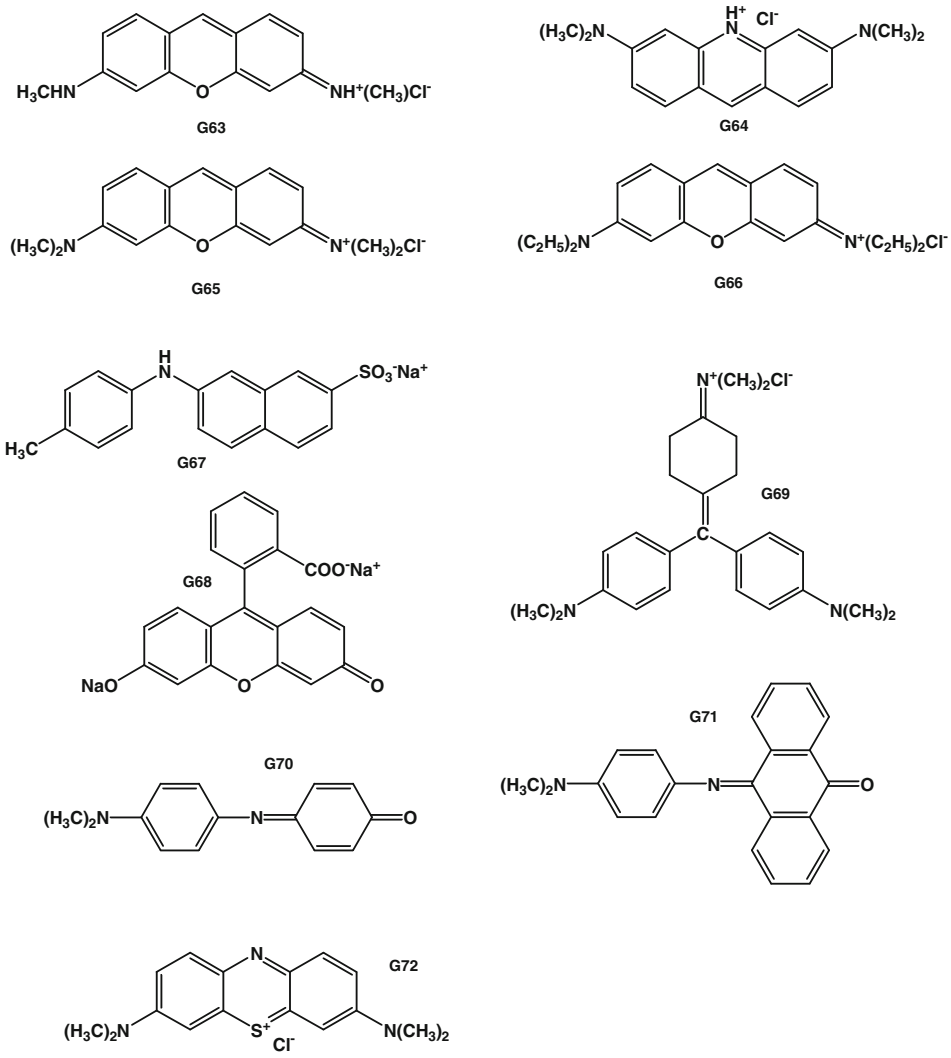
the stronger binding ability of the complex with H1 than H22 is attributed to the effective C–Hπ interactions.

Binding with dye molecules

Our group have investigated the interactions of some dye guest molecules (G63–G69) (Scheme 6) with a series of p-sulfonatocalixarenes (H1, H3, H4, H13, H15, H16, H19, H21) by the method of fluorescence spectroscopy [57]. The results show that H1, H3 and H4 could form stable complexes with G63, G65 and G66, showing similar molecular selectivity. The binding constants monotonically increase with increasing the ring size. G63 could also form stable complexes with alkylated sulfonatocalixarenes at lower rim. The binding constants increase with the length of the hydrophobic alkyl chain. G67 could not form stable complexes with sulfonatocalixarenes because of the electrostatic repulsion between the sulfonate groups of G67 and p-sulfonatocalixarenes.

Barra and Shinkai et al. studied the interactions of G70 (Scheme 6) with a series of p-sulfonatocalixarenes (H1, H3, H4, H12 and H14) [4, 7, 58, 59]. The results show that the binding constants increase in the order of H1 < H3 $\approx$ H4, indicating that the larger host cavity can accommodate the guest molecule better. The complexation of G70 with H1, H3, H4 and H12 is driven by favorable enthalpy change arising from hydrogen bonding and/or strong electrostatic interactions, however, in the case of H14, the complexation is driven by an increase in entropy because the loss of the arrangement of water molecules prevails in this case. The interactions of p-sulfonatocalixarenes (H18–H20) with G70 and G71 (Scheme 6) were further investigated by Shinkai et al., which established that the calixarene cavity was capable of molecular recognition on the basis of the 'hole-size selectivity' for the first time [60]. G70 and G71 could form 1:1 complexes with these hosts accompanied with different host selectivity. The selectivity for G70 (small guest molecule) is in the order of H19 >

Scheme 6 Structures of dye guests G63–G72



H18 > H20, whereas the order is H20 > H19 > H18 for the larger guest molecule G71.

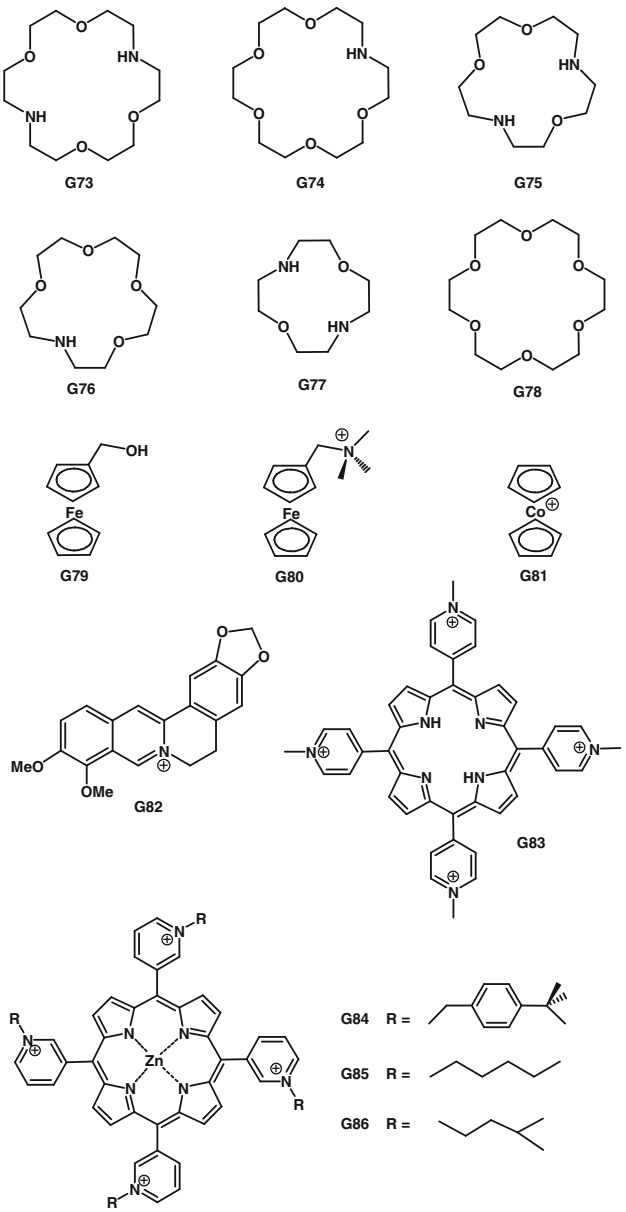
Sueishi et al. investigated the interactions of G72 with H1, H3 and H4 [61], which showed that H3 and H4 could form 1:1 complexes with G72 whereas the stoichiometry for the complex of H1 with G72 was 2:1. The binding ability of H4 is stronger than that of H3, which implies that G72 is t better to the cavity of H4 than to that of H3. The guest is included into the host cavity from $-N(CH_3)_2$ moiety. Compared with H1, H3 accommodates G72 into its cavity more deeply. H4 includes this guest from two sides. As the external pressure increases, the inclusion equilibrium of G72 with H1 and H3 shifts to the dissociation side whereas the inclusion equilibrium with H4 shifts to the association side.

Others

Besides the aforementioned conventional guest molecules, p-sulfonatocalixarenes can also form inclusion complexes with several specific substrates, such as amino acids and peptides [9, 62–65], testosterone [66], steroids [67], tetracaine [68], lomefloxacin [69], BSA (Bovine Serum Albumin) [70, 71], fullerene, crown ethers, porphyrin, Ru complex, ferrocene, and so on (Scheme 7). The interactions of p-sulfonatocalixarenes with some biological/pharmic molecules have just been reviewed by Colemana et al. [3b], which will not be further described herein.

Kunsági-Máté et al. studied the interactions of C_{60}-fullerene and its derivatives with H3 and H22 by means of photoluminescence and quantum-chemical methods in neutral conditions [72]. They found that H22 and C_{60} could form a stoichiometric 2:1 complex while the stoichiometry of the complex of H3 with C_{60} is 1:1. The complexation is mainly driven by favorable enthalpy changes, accompanied by negative entropy changes. C_{60}-fullerene is included in a cavity composed of two half-bowl molecules of H22 and it is located much more deeply in the cavity of H3, which inhibits the formation of the bowl-shaped capsule due to the negatively charged sulfonate groups.

The inclusion properties of H1 upon complexation with crown ether species (G73–G78) in aqueous solution were investigated by Raston and co-workers utilizing the method of diffusion-ordered ^{1}H NMR spectroscopy [73]. The results show that neutral 18-crown-6 G78 is not bound with H1 while G78 Na^+ can be included into the cavity of H1 with $K_S \approx 3.1 \times 10^3\ M^{-1}$. The charged azacrown ethers examined (G73–G77) can be bound by H1 with K_S values from 5.1×10^2 to $9.9 \times 10^5\ M^{-1}$. These observations explain the phenomena of rapid capture of azacrown ethers in molecular capsules based on H1/lanthanide metals and the formation of "Russian doll" superanions in the solution phase well.



Scheme 7 Structures of crown ether, electroactive guests, berberine and porphyrin guests G73–G86

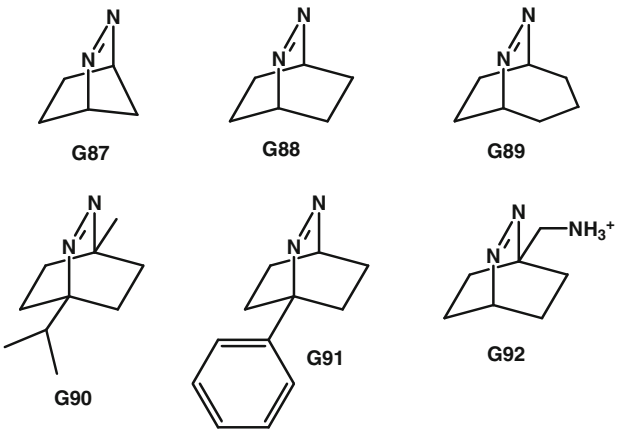
Kaifer and co-workers studied the interactions of electroactive guests (G79–G81) with H3 in aqueous solutions [74], which showed that all the three guests used could form complexes with H3 and the stabilities of the complexes increased with the number of positive charges on the guests although the uncharged guests could also interact with the host. At neutral condition, H3 could form quite stable complexes with either two G80 or two G81 guests with its 1,2,3-alternate conformation. The stabilities of the complexes containing ferrocene decrease dramatically at pH 2.6 compared with at pH 7.0. Kitamura and co-workers reported that H3 and tris(2,2′-bipyridine)ruthenium(II) dication could form a stoichiometric 1:2 hybrid

complex and it could be used as a new class of chemo sensor [75].

Megyesi and Bicźk investigated the interactions of berberine (G82) with H1, H3 and H4 in aqueous solution [76]. Stoichiometric 1:1 complexes are formed between host and guest, in which hydrophobic and p interactions as well as electrostatic attraction are the driving forces fo the complexation. The size of the host cavity is the dominant factor determining the binding constant. The complex of H4 with G82 gives the largest binding constant due to the high exibility of H4 and its comparable size to G82. The stabilities of the complexes will signi cantly diminish when the size of host ring becomes smaller, and thereb H1 shows the weakest binding ability. The effect of pH to the complexation of G82 with p-sulfonatocalixarenes is less important, which implies that the Coulomb force is not the dominant factor in this process.

Sciotto and co-workers reported that H5 and cationic porphyrin G83 could form stable supramolecular complexes of 4:5 or 4:3 stoichiometry both in solid state and in aqueous solution, and the protonation state of carboxylate groups of H5 determined the stoichiometry of the complexes [77]. Interestingly, the formation of H5 G83 complex can be stepwise progress, which opens new frontiers of noncovalent synthesis to design speci c multiporphyrin aggregates having a wide range of possible application [78]. Reinhoudt and co-workers reported that H6 and cationic porphyrin guests G84–G86 could form self-assembled cage-like complexes with remarkable stability via an entropy-driven process in polar solvents [79]. Furthermore, they found that the formation of cage-like complexes between H6 and the peptide-attached cationic porphyrins could also be achieved, which could further form ternary complexes upon addition of suitable ligands [80]. Such structures can be used as heme-protein active site models for the evolution from structural to functional models of heme-proteins. Lang et al. studied the interactions of H1, H3 and H4 with G83 [81]. The results showed that H1 and G83 could form a stoichiometric 1:1 complex with a high binding af nity while the other two hosts could form stoichiometric 1:2 complexes with G83. The driving force for the formation of the complexes is electrostatic interactions between the host and guest. The structure o the H1 G83 complex can also be a cage-like complex with the porphyrin moiety atop the calixarene upper rim. Moreover, intermolecular photo-induced electron transfe from calixarene to porphyrin exists in the course of complexation.

Nau and co-workers investigated the binding behavio of H1 with a series of bicyclic azoalkane guests (G87–G92) (Scheme 8), which is further promised to apply as uorescent monitors and metalloenzyme models. The binding abilities and geometries between H1 and



Scheme 8 Structures of bicyclic azoalkane guests G87–G92

G87–G91 were systemically studied by NMR spectroscopy in pD 7.4 D_2O [82]. All the guests could form 1:1 complexes with H1. In the case of G87–G89, they are bond to H1 with an equatorial complex geometry as a result that the polar azo group points toward the aqueous bulk and the hydrophobic part of the bicycle can ef ciently interact with H1 through C–H p interactions, and then show a moderately strong binding with H1 exceptionally. In the case of G90 and G91, an axial inclusion mode is observed and the isopropyl group of G90 and the azo bicyclic residue of G91 are preferentially included into the host cavity. Therefore, although G91 and G92 are more hydrophobic than G87–G89, they are bond to H1 more weakly. Especially, upon complexation with G91, H1 presents the distinct inclusion geometry from b-cyclodextrin (Fig. 7), which indicates that spherical shape complementarity between the guest and the conical cavity offered by H1 is rather important for the complexation than the hydrophobic and p interactions offered by aromatic guests. The complexation of H1 with bicyclic azoalkanes is pH-dependent that H1 can bind protonated azoalkanes more strongly than neutral ones, and then shows the increased binding constants in acidic

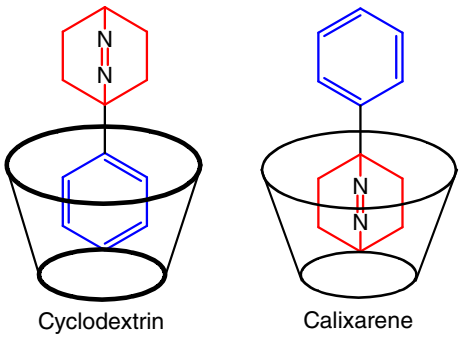


Fig. 7 The different inclusion geometries of G91 with b-cyclodextrin and H1

solution (pD 2.4) [83]. However, the binding constants decrease again in more highly acidic solutions because of the competitive binding by the hydronium ion. Moreover, the complexation of H1 can induce the pK_a shifts of azoalkanes by around 2 unites, resembling the enzyme mimetic action.

Signi cantly, the calixarene-azoalkane species opened a new uorescence-based method to sensitively monitor and quantify the binding of inorganic cations and organic ammonium ions by H1 in aqueous solutions at different pH based on competitive binding involving the displacement of a uorescent azoalkane G88 [84, 85]. Differing from the competitive binding, the cooperative binding leads to the formation of the ternary complex of calixarene, metal ions, and azoalkane, which constructs interesting structural metalloenzyme models in aqueous solution based on dynamic self-assembly (Fig. 8) [86]. Furthermore, Nau and co-workers reported a new economic, convenient and general assay principle based on calixarene-azoalkane system, in which amino acid decarboxylase activity could be continuously monitored by measuring changes in uorescence, attributing to the competition of the enzymatic product and G92 for forming a complex with H1 (Fig. 9) [87].

Applications

In the preceding sections, we have gained a deep insight into the structures and binding properties of sulfonatocalixarenes, which has endowed them potential applications in several elds, including the sensor/probe, catalysis, micro-reactor, enzyme-mimic/enzyme-assay (mentioned above, ref. 86 and 87), surfactants, and so on besides the crystal engineering and biochemistry reviewed by Atwood, Raston and Coleman et al. [3].

According to the outstanding properties of sulfonatocalixarenes, such as low K_a values, cation p interactions, high water-solubility, Shinkai and co-workers exploited a new arti cial acetylcholine detection system useful in neutral aqueous (water/methanol) solution (Fig. 10). This improves uorescent sensing system and supplies a convenient way to selective and nondestructive histochemical analysis of acetylcholine against amino acids in a biological system [88]. Based on the uorescence complex H3 with CTAB (cationic surfactant cetyltrimethylammonium bromide), a new method for assaying CTRX (ceftriaxone sodium) in pharmaceutical preparations was developed, which provided valuable information for pharmaceutical and biomedical analysis by employing p-sulfonatocalixarenes [89].

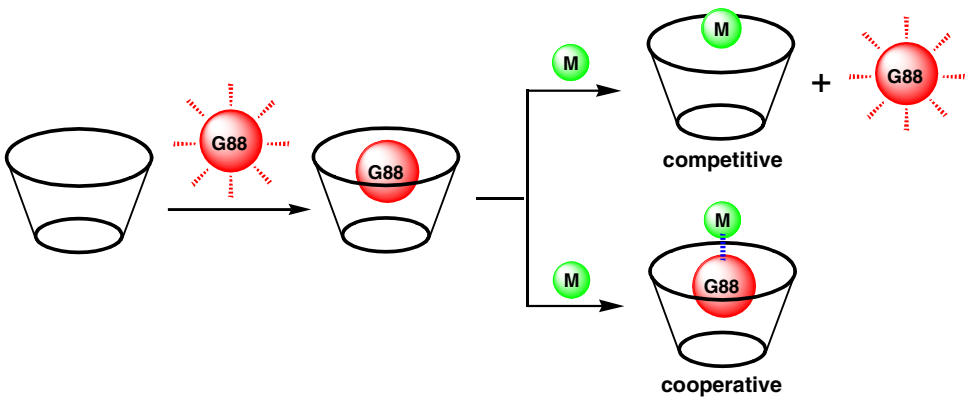


Fig. 8 Competitive uorephore model and cooperative metalloenzyme model based on H1 G88 complex

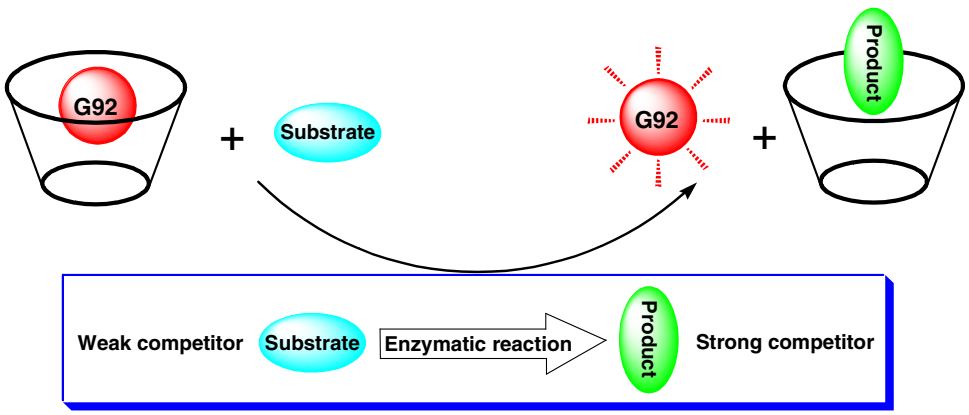


Fig. 9 Illustration of label-free continuous enzyme assays with H1 G92 complex

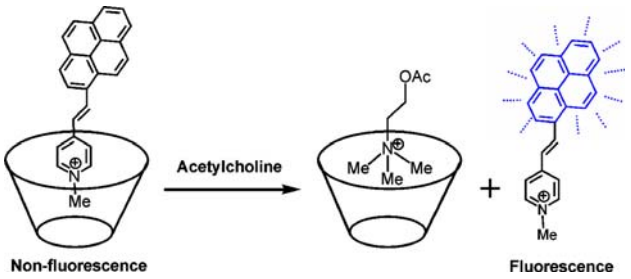


Fig. 10 The artificial acetylcholine detection system based on p-sulfonatocalixarenes

Bobacka and co-workers studied the potentiometric sensing behavior for metal ions by galvanostatic electropolymerization of 3,4-ethylenedioxythiophene and pyrrole on glassy carbon electrodes utilizing p-sulfonatocalixarenes as dopants, which found that the conducting polymer and dopant combinations possessed preferable sensitivity and selectivity for Ag^{+} rather than alkali, alkaline-earth, and other transition-metal ions [90]. H25 can be applied to a capillary electrophoresis microchip for the selective detection of uranium(VI) [91]. Valeur and co-workers reported a synthesized host compound H24 in the 1,3-alternate conformation [92]. They found that this host could be used as a water-soluble fluorescent molecular sensor to selectively detect cesium ions. Yoshida and co-workers reported the solvent extraction of UO_2^{2+} by using p-sulfonatocalixarenes (mainly H3 and H4) with high selectivity in the presence of trioctylmethylammonium-chloride [93]. The extractability increases with the stability of the complex in aqueous solution. Miyano and co-workers reported not only H1 but also its analogous H22 and H23 could form complexes with Tb^{3+} and the resulting complexes exhibited strong energy transfer luminescence [14, 94]. The complexation ability of H22 and H23 towards Tb^{3+} is higher than that of H1. H22 and H23 may be used as candidates to construct luminescence devices due to their complexation ability and luminescent performance. H23 could be used as highly selective luminescence determination of Tb^{3+} at the sub-ppb level. Chen and co-workers reported that H1 could be applied as a selector to separate phenolic positional isomers in capillary electrophoresis utilizing the partial filling technique, which mainly derived from the inclusion complexation interactions between host and guest, including hydrophobic, C–H π, and O–H π interactions [95].

Early in 1986, Shinkai et al. found that H3 and its derivatives (H11, H12, H14 and H17) could markedly accelerate acid-catalyzed hydration of 1-benzyl-1,4-dihydronicotinamide. Particularly, the rate constants improved by H3 and H11 are 2–3 orders of magnitude higher than those by noncyclic analogue p-(hydroxybenzenesulfonate and p-(carboxymethoxy)benzenesulfonate) as they both have acidic protons to catalyze the reaction and anionic sulfonates to stabilize the cationic intermediate at the two edges of the cavity [7]. Ueoka and co-workers reported that p-sulfonatocalixarenes (H1, H3 and H4) possessed specifically catalytic activity in the alcoholysis of N-acetyl-L-amino acids [96]. Dramatically, the methanolysis rates of basic amino acid substrates are effectively enhanced by p-sulfonatocalixarenes for His, Lys, and Arg substrates, while not for Phe, Tyr, and Trp substrates. In addition, the methanolysis of the His substrate catalyzed by H1 and H3 obeys Michaelis–Menten kinetics, which indicates that the catalytic capability of p-sulfonatocalixarenes originates from the complexation with specific substrates, resembling the enzymatic reactions. Tao and Barra reported that the deamination of quinone-imine dye in basic aqueous solution was inhibited when it was complexed with p-sulfonatocalixarenes, such as H1, H3 and H12 [97]. Ramamurthy and co-workers reported that H3 and H4 could act as template to promote the dimerization of trans-stilbazoles [98]. Photolysis experiments at the same concentration of substrates show that the employed stilbazoles mainly isomerize to the corresponding cis isomers in the absence of H3 or H4, whereas they can form anti-head-tail dimers in the presence of H3 or H4. It is owing to that p-sulfonatocalixarenes contribute to localize and orient the substrates in a specific geometry through the host–guest electrostatic and hydrophobic interactions. As a result, they explored a model of application of p-sulfonatocalixarenes as reaction vessels in water.

Furthermore, p-sulfonatocalixarenes can act as "surfactants with a host–guest-type recognition site" once proper aliphatic chains are appended at the lower-rim [7]. For example, the aggregation behavior of H14 and H17 in water was determined by the measurements of light-scattering, surface tension, conductance, fluorescence and absorption spectroscopies, which established that H14 had a CMC (critical micelle concentration) at ca. 6×10^{-4} M, while H17 had no detectable CMC and rather acted as a "unimolecular" micelle. Utilizing spinning disk progressing, Makha and co-workers compared the nanoparticles of trans-b-carotene in the presence of macrocyclic amphiphiles, p-sulfonatocalixarenes and cyclodextrins [99]. The results obtained implied that the carotene nanoparticles formed with p-sulfonatocalixarenes were stable with respect to extraction of the carotene into an organic solvent, differing from those with cyclodextrins.

Conclusions and outlook

In conclusion, we have summarized the binding structures and properties of p-sulfonatocalixarenes with various guest molecules, their thermodynamic origins and some typical

applications in this review. Possessing the particular structures of 3D cavity and additional binding site of sulfonate groups, *p*-sulfonatocalixarenes can extensively form inclusion complexes with not only inorganic cations but also organic cations/neutral molecules, showing distinguishable binding abilities and selectivities. Furthermore, these pronounced inclusion properties endow them versatile applications in many fields, including crystal engineering, biochemistry, sensor/probe, catalysis, and so on. However, we believe that the exciting functions and potentials of *p*-sulfonatocalixarenes are still attracting more and more scientist's interests in the years to come. In the future respect we are pursuing, two investigation directions are promised to deserve particular attention: (a) the preparation of *p*-sulfonatocalixarene derivatives modified with various functional groups and construction of highly nano-supramolecular assemblies; (b) applications of solar energy conversion, photolithography, molecular photonics, and phototriggering based on PET (photoinduced electron transfer) progress from the electron-rich *p*-sulfonatocalixarenes to electron-poor antenna guests with light-harvesting capability.

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