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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 π-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 influenced 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 briefly described.

Keywords *p*-Sulfonatocalixarenes · Complexation · Structures · Thermodynamics

Introduction

Calixarenes represent a particularly significant class of the host molecules in supramolecular chemistry, which are described as 'macrocycles with (almost) unlimited possibilities' for their facile modification [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 five 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, flexible, π-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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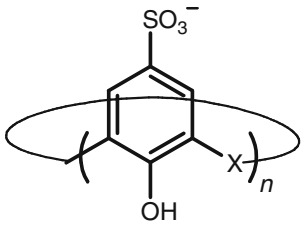


C4AS: X = CH_2, $n = 4$
TC4AS: X = S, $n = 4$
C5AS: X = CH_2, $n = 5$
C6AS: X = CH_2, $n = 6$
C8AS: X = CH_2, $n = 8$

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 ($\Delta H°$ 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$\cdots\pi$ interactions. Herein, it should be mentioned that the $Tl^+\cdots\pi$ 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

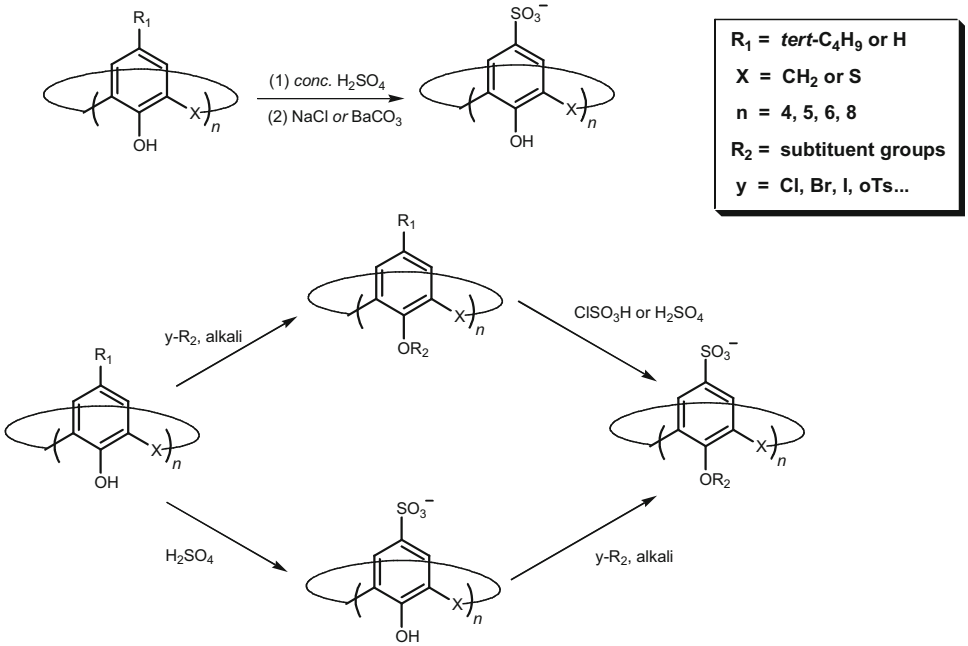
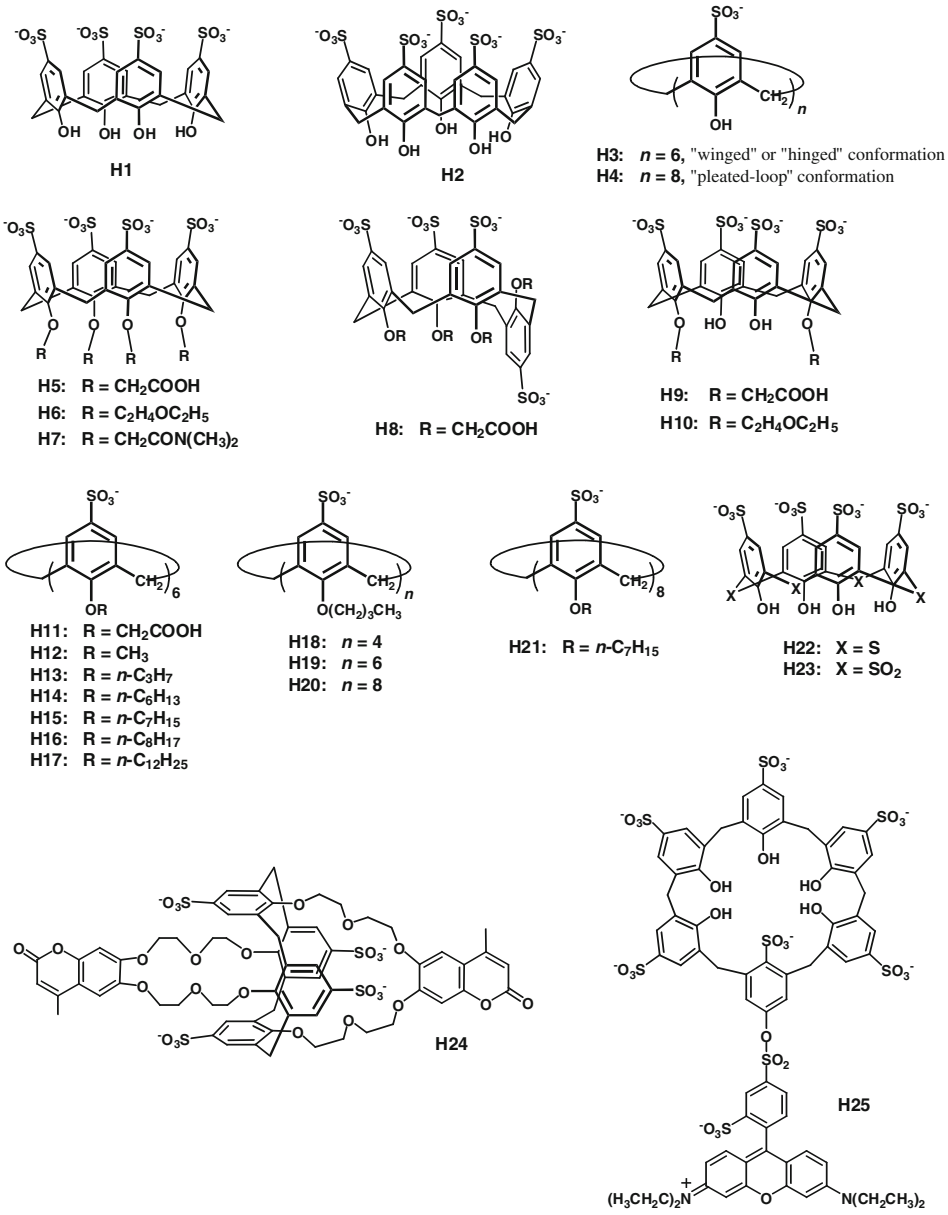


Fig. 1 The synthetic routes of *p*-sulfonatocalixarenes and their derivatives

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 M^{n+} 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 (La^{3+}, 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 flexibility 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 ($\Delta H°/(kJ\ mol^{-1})$), 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	lgK_S	$\Delta H°$	$T\Delta S°$	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.

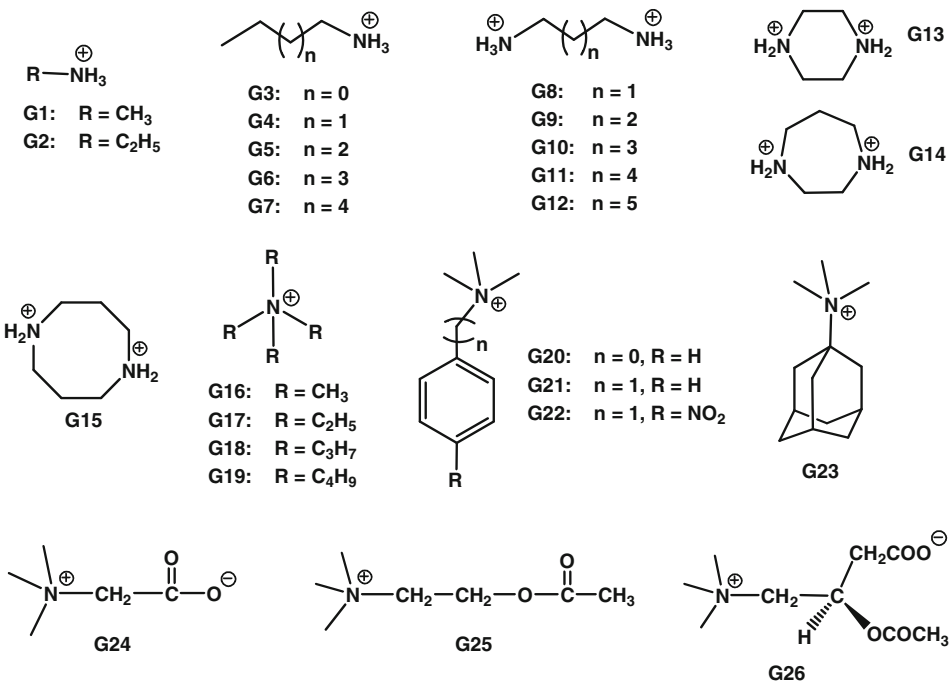
Yoshida and co-workers studied the interactions of **H4** with divalent metal ions (Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and UO_2^{2+}) in aqueous solution by the method of pH titration [19]. The results obtained show that Cu^{2+} cannot form complex with **H4**. All the other 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 π-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 π-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. It 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–fit relationship and pH value are two significant 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–fit 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 fits the size of diazacycloalkane guests better.

Shinkai et al. firstly 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 flexible 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 field. 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 efficiently. 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 ($\Delta H°/(kJ\ mol^{-1})$), and entropy changes ($T\Delta S°/(kJ\ mol^{-1})$) for intermolecular complexation of organic ammonium cations with *p*-sulfonatocalixarenes in aqueous solution at 298.15 K

Hosts	Cations	pH	lgK_S	$\Delta H°$	$T\Delta S°$	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 significant heat effect

[a] lgK_{S1}

[b] lgK_{S2}

more hydrophobic property of the adamantly group. **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 fit recognition is often more efficient 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···π 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 $\pi\cdots\pi$ and electrostatic or C–H···π and electrostatic interactions) synchronously to capture **G20** and **G21**, whereas **H2** provides a synergy of three interactions ($\pi\cdots\pi$, C–H···π 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 $\pi\cdots\pi$ interaction. In contrast, the binding stability of **H1** with **G22** is comparable with **G21** because $\pi\cdots\pi$ 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**)

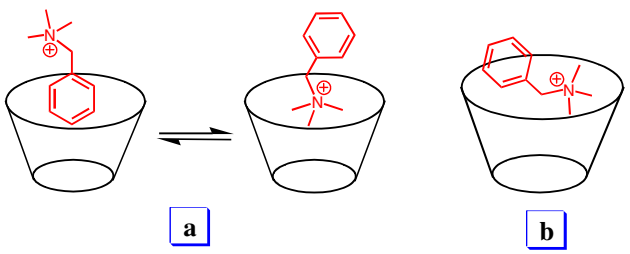


Fig. 2 Binding manners of **G21** with **H1** (**a**) and **H2** (**b**)

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 flexibility of **H1** and a mobility of the cation. Upon complexation with these organic ammonium cations, the cavity of **H1** becomes more open.

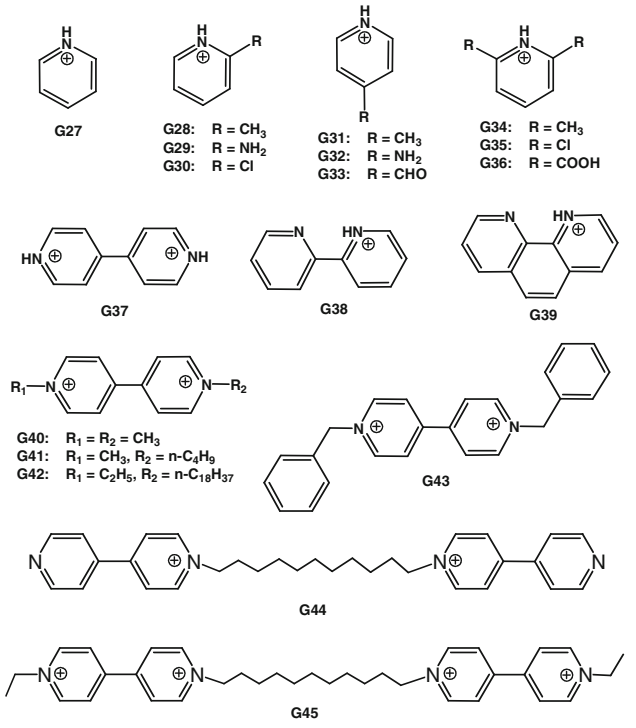
Our group have also studied the interactions of some quaternary ammonium cations (**G21**, and **G24–G26**) with **H1**, **H3** and **H22** in pH 7.2 phosphate buffer solutions at 298.15 K using calorimetric titration and NMR experiments [29]. All the guests and *p*-sulfonatocalixarenes employed could 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 π-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

smallest cavity and relatively high π-electron density that contribute to the good size–fit and strong C–H$\cdots\pi/\pi\cdots\pi$ 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 $\pi\cdots\pi$ 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 fluoremetric 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 3) [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 π-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$\cdots\pi$ 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. π-Stacking, especially C–H$\cdots\pi$, 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 π-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 ($\Delta H°/(kJ\ mol^{-1})$), 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	lgK_S	$\Delta H°$	$T\Delta S°$	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 significant heat effect

[a] lgK_{S1}

[b] lgK_{S2}

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

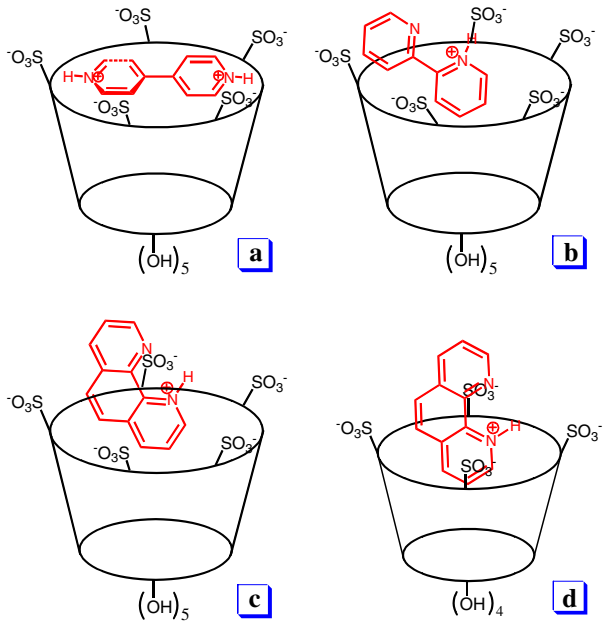


Fig. 3 Deduced binding modes of guests **G37–G39** with **H1** and **H2**

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 [41], widely used in many fields, such as herbicides [42], probes to study DNA and zeolites [43], subunits in constructing functional molecular assemblies/machines [44], 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

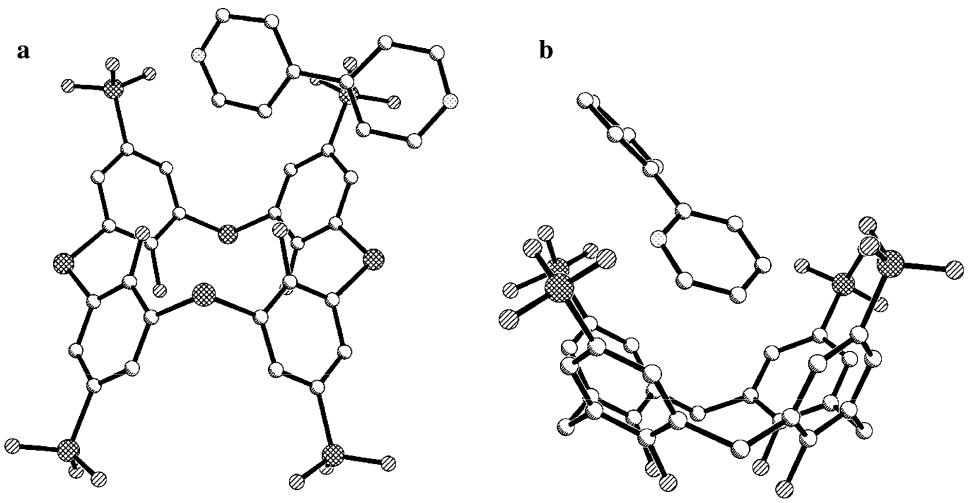


Fig. 4 The solid-state structures of **H22**·**G37** (**a**) and **H1**·**G38** (**b**)

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 affinity 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···π and π···π interactions. The second binding constant is less than the first one due to a less enthalpy contribution resulting from weak C–H···π, C–H···O and van der Waals interactions although the entropy loss in the second step is less than the first 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 firstly 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 π-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 confirmed by cyclic voltammetry. However, the binding affinities of **H1** or **H2** with the radical cation of **G40** are obviously weaker than those with **G40** due to the weaker π-electron acceptor and hydrogen-bonding donor abilities of its radical cation.

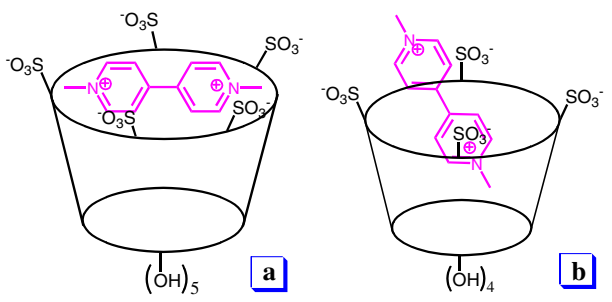
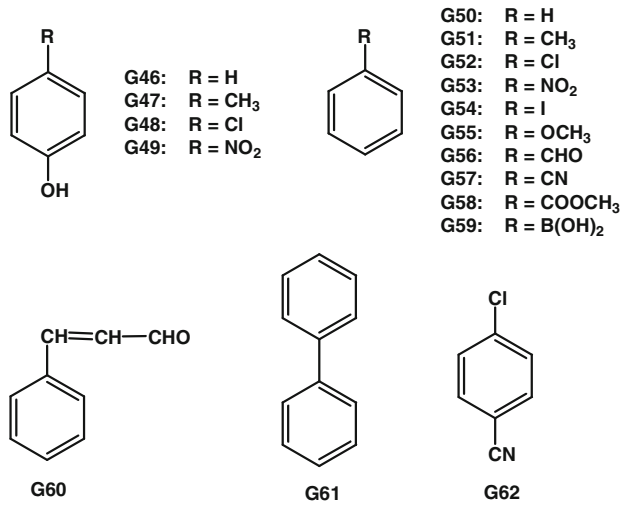


Fig. 5 Deduced binding manners of **H2** (**a**) and **H1** (**b**) with **G40**

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 *n*-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 $\pi\cdots\pi$ 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 five aromatic protons are pointing inside and the functional group of guest is located outside the cavities of hosts due to hydrophobic and $\pi\cdots\pi$ 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$\cdots\pi$ 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$\cdots\pi$ 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 $\pi\cdots\pi$ interaction plays an important role in the complexation. **H22**, with lower electron density and larger cavity than **H1**, is more efficient 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**,

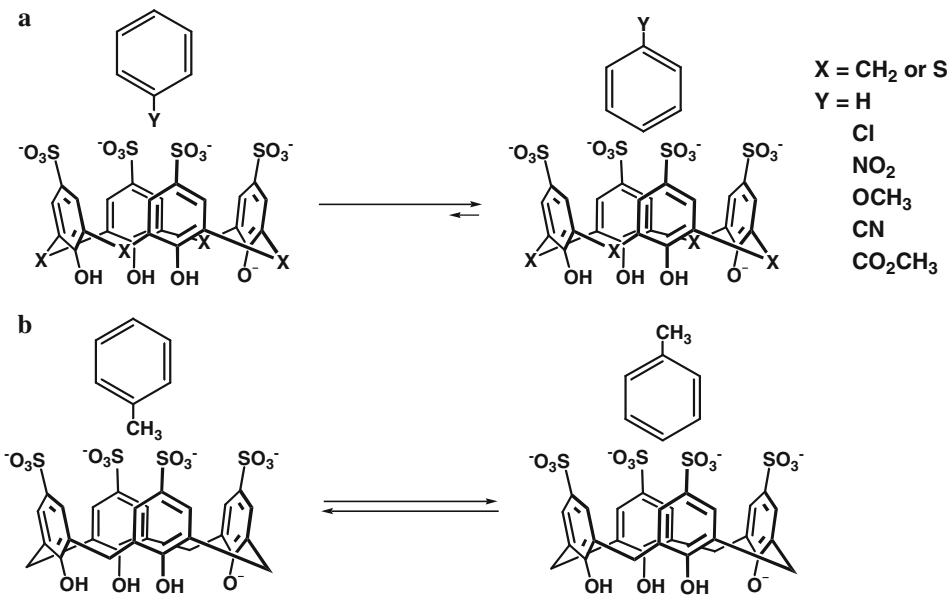


Fig. 6 Complexation modes of **H1** and **H22** towards mono-substituted benzenes (**a**) except that of **H1** towards **G51** (**b**)

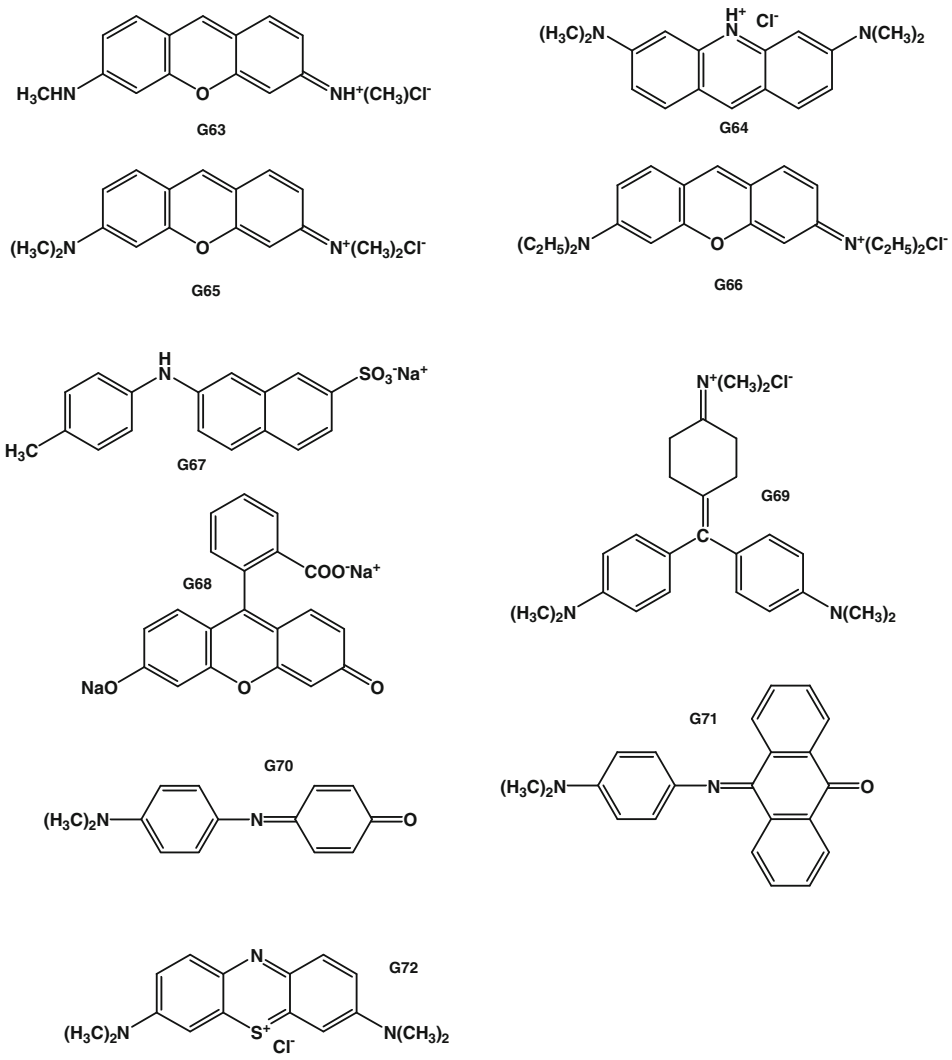
the stronger binding ability of the complex with **H1** than **H22** is attributed to the effective C–H···π interactions.

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 in **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** ≈ **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**.

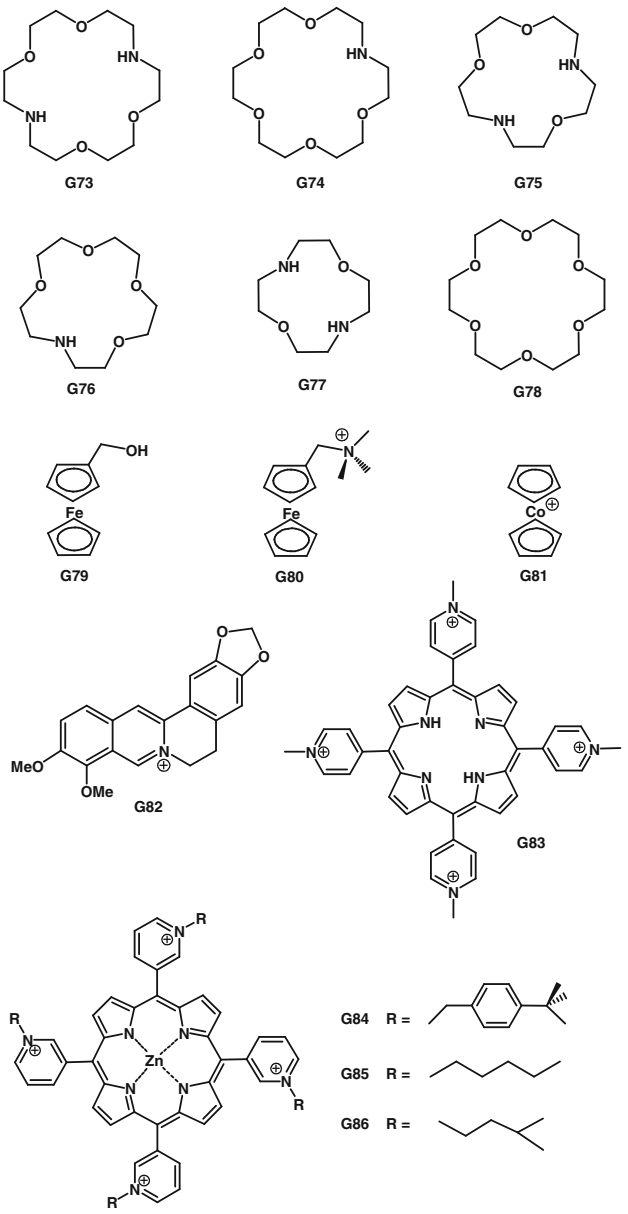
Sueishi et al. investigated the interactions of **G72** with **H1**, **H3** and **H4** [61], which showed that **H3** and **H4** could form 1:1 complexes with **G72** whereas the stoichiometry for the complex of **H1** with **G72** was 2:1. The binding ability of **H4** is stronger than that of **H3**, which implies that **G72** is fit 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 Coleman 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**

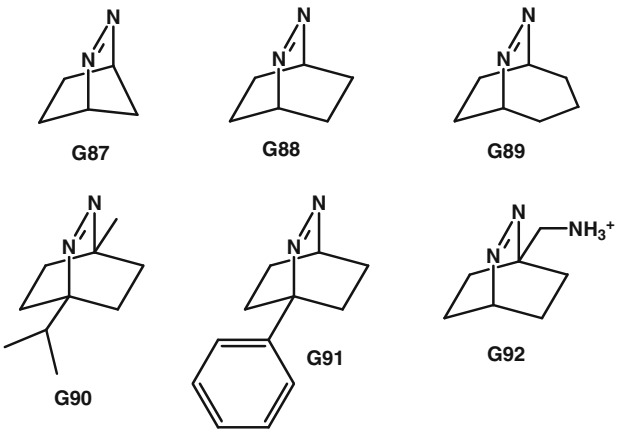
Kaifer and co-workers studied the interactions of electroactive guests (**G79–G81**) with **H3** in aqueous solutions [74], which showed that all the three guests used could form complexes with **H3** and the stabilities of the complexes increased with the number of positive charges on the guests although 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 chemosensor [75].

Megyesi and Biczók 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 $\pi\cdots\pi$ interactions as well as electrostatic attraction are the driving forces for 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 flexibility of **H4** and its comparable size to **G82**. The stabilities of the complexes will significantly diminish when the size of host ring becomes smaller, and thereby **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 specific 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 affinity 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 of 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 transfer from calixarene to porphyrin exists in the course of complexation.

Nau and co-workers investigated the binding behavior of **H1** with a series of bicyclic azoalkane guests (**G87**–**G92**) (Scheme 8), which is further promised to apply as fluorescent 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 efficiently interact with **H1** through C–H$\cdots\pi$ 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 *β*-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 $\pi\cdots\pi$ 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

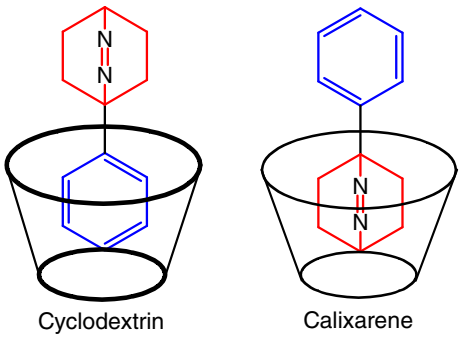


Fig. 7 The different inclusion geometries of **G91** with *β*-cyclodextrin and **H1**

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.

Significantly, the calixarene-azoalkane species opened a new fluorescence-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 fluorescent 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 fluorescence, 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 *p*-sulfonatocalixarenes, which has endowed them potential applications in several fields, 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 *p*-sulfonatocalixarenes, such as low pK_a values, cation$\cdots\pi$ interactions, high water-solubility, Shinkai and co-workers exploited a new artificial acetylcholine detection system useful in neutral aqueous (water/methanol) solution (Fig. 10). This improves fluorescent 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 fluorescence complex of **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].

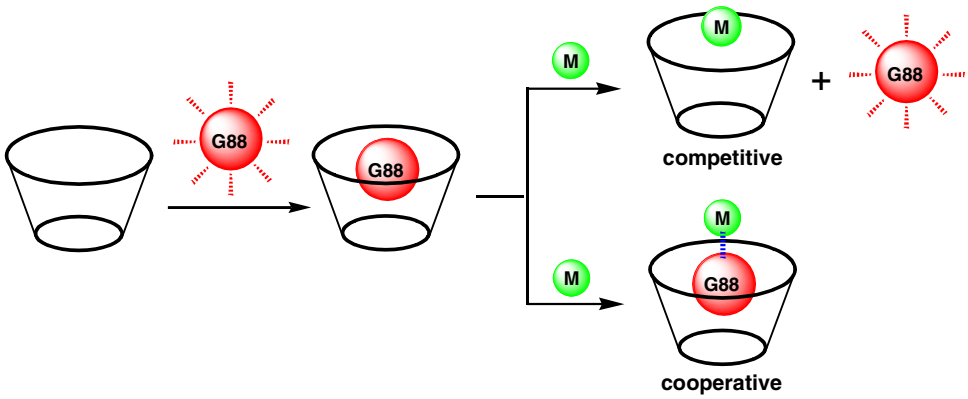


Fig. 8 Competitive fluorephore model and cooperative metalloenzyme model based on **H1**·**G88** complex

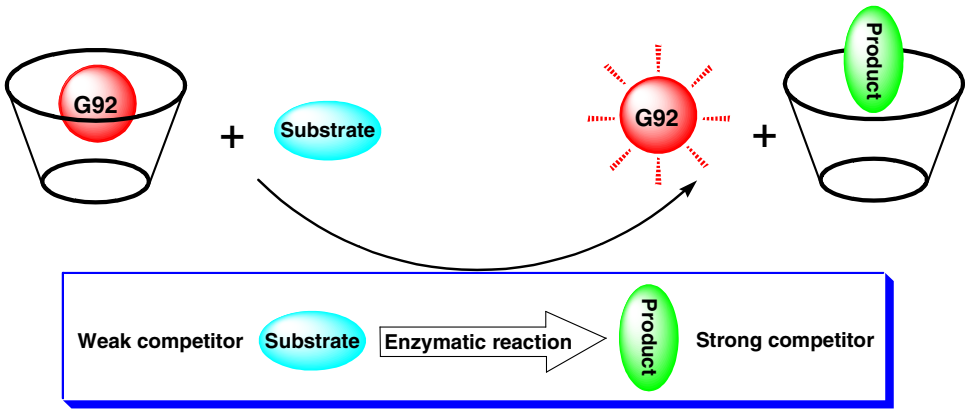


Fig. 9 Illustration of label-free continuous enzyme assays with **H1**·**G92** complex

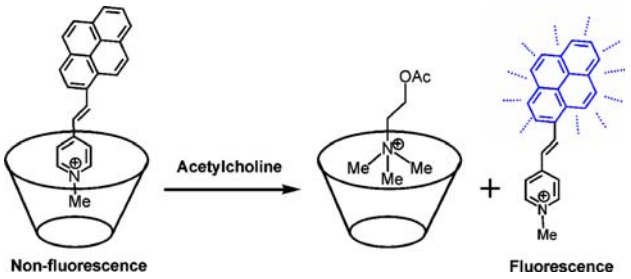


Fig. 10 The artificial acetylcholine detection system based on *p*-sulfonatocalixarenes

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$\cdots\pi$, and O–H$\cdots\pi$ 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 analogues (*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 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 stibazoles 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-β-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 nanosupramolecular 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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