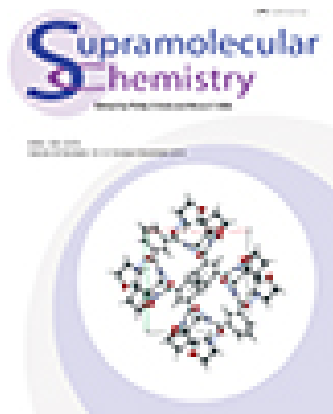


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Binding behaviour and solubilisation of *p*-sulfonatocalixarenes to cinchona alkaloids

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In this study, we investigated the binding behaviours of three water-soluble *p*-sulfonatocalixarenes with four cinchona alkaloids in aqueous and phosphate buffer solutions (pH 7.2 and 2.0). The complexation stability constants obtained by fluorescence titrations were comparatively discussed from several aspects: host cavity, pH effect and ionic strength. Among three hosts, *p*-sulfonatocalix[4]arene (SC4A) forms the most stable complexes with cinchona alkaloids, especially in acidic aqueous conditions. Furthermore, SC4A was elected as model drug carrier for cinchona alkaloids, where solubilisation by the complexation of SC4A and mimic release from the calixarene cavity in the presence of negatively charged micelles were initially studied.

Keywords: calixarene; cinchona alkaloids; host–guest complexation; solubilisation

Introduction

Calixarenes (1), composed of phenolic units linked by methylene groups, represent one of the most widely studied classes of organic supramolecular hosts and are described as ‘macrocycles with (almost) unlimited possibilities’ due to their facile modification. In most cases, they serve as simple scaffolds to build podand-like receptors where the calixarene cavity very often remains unexploited (2). Extensive chemical modification of maternal calixarene is always demanded to achieve the desired *endo*-complexation (3).

p-Sulfonatocalix[*n*]arenes (SC*n*As, *n* = 4–8) (4), sulfonated directly on the upper rim, represent a family of water-soluble calixarene derivatives with robust cavity-binding properties in aqueous media. SC*n*As are able to complex with numerous guest molecules, especially organic cations, driven by the synergistic effect of intrinsic π -electron-rich cavities together with the additional anchoring points donated by sulfonated groups (5). Benefitting from the improved binding properties, SC*n*As have gained considerable attention in the fields of molecular recognition/sensing (6), crystal engineering (7), catalysis (8), amphiphiles (9), enzyme-mimics/enzyme-assays (10), drug solubilisation (11) and medicinal chemistry (12). It is worth mentioning that SC*n*As are demonstrated to be bio-compatible (13). *In vitro*, SC4A shows zero haemolytic toxicity for concentrations up to 5 mM and a lack of non-specific immune response. *In vivo*, SC4A shows no acute toxicity for single injected doses

equivalent to 2–5 g in humans and is rapid cleared *via* elimination in urine without accumulation in the liver. Such intrinsic bio-compatibility directs SC*n*As to pharmaceutical applications, such as complexation of pharmacologically active compounds (14). Such host–guest complexes have been investigated in view of their potential use as new therapeutic formulations designed to increase the bioavailability and/or to decrease the systemic toxicity of the biologically active compounds (15).

Cinchona alkaloids, natural products typically extracted from the bark of *Cinchona ledgeriana* trees, have proven quite versatile (16). They are used to treat malaria and cardiac arrhythmias (17), as chiral modifiers in heterogeneous catalysis (18) and as flavours in food and drinks (19). However, their low aqueous solubility becomes an obstacle in their applications. For example, low aqueous solubility will potentially reduce the dissolution rate of the drug in the gastrointestinal tract, which is the first step for absorption of the drug by the body (20). Moreover, inaccurate dosage will cause a series of side-effects such as headache, diarrhoea, rash and even death. Thus, efficient carriers are necessary to guarantee their efficient applications.

In this study, we wish to report our research on binding behaviours of SC*n*As with cinchona alkaloids in different biological environments, such as serum (pH 7.2) or gastric acid (pH 2.0), to gain insight into the association and release process and to explore their potential application in drug delivery.

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Experimental

Materials

All chemicals used are reagent grade unless noted otherwise. Quinine, quinidine, cinchonine and cinchonidine were purchased from commercial resources and used without further purification. *p*-Sulfonatocalix[4]arene (SC4A), *p*-sulfonatocalix[5]arene (SC5A) and *p*-sulfonatothiacalix[4]arene (STC4A) were synthesised and purified according to reported procedures (21).

The phosphate buffer solution of pH 7.2 was prepared by dissolving disodium hydrogen phosphate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$, 25.79 g) and sodium dihydrogen phosphate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 4.37 g) in distilled, deionised water (1000 ml) to make a 0.1 M solution. The phosphate buffer solution of pH 2.0 was prepared by dissolving sodium dihydrogen phosphate in distilled, deionised water to make a 0.1 M solution, which is then adjusted to pH 2.0 by phosphoric acid. Solutions at pH 7.2 and pH 2.0 were prepared with distilled, deionised water and adjusted with 1.0 M sodium hydroxide (NaOH) or 1.0 M hydrochloric acid (HCl) and verified on a pH meter calibrated.

Instruments and measurements

Fluorescence titration

Fluorescence spectra were recorded in a conventional quartz cell (10 mm \times 10 mm \times 45 mm) at 25°C on a VARIAN CARY Eclipse spectrometer (Agilent Technologies, Inc., USA) with the excitation and emission slits of 5 nm width for quinine and quinidine both at pH 7.2 and pH 2.0. While the excitation and emission slits of cinchonine and cinchonidine were 10 nm wide at pH 7.2 and 5–10 nm wide, respectively, at pH 2.0. The excitation wavelength for quinine, quinidine, cinchonine and cinchonidine is 329 nm, and the maximum emission wavelength is 387 nm. The sample solutions containing cinchona alkaloids (1.0×10^{-5} M) and various concentration of hosts ($(0-4.0) \times 10^{-3}$ M) were maintained at 25.0°C ($\pm 0.1^\circ\text{C}$) for spectral measurements by a circulating thermostated water-jacket. Fluorescence spec-

tra changes were observed and the stability constants of the resulting complexes were calculated using fitting functions by the nonlinear least square method.

Solubilisation

Solubility enhancement studies were carried out using the phase solubility method. Solutions containing known concentrations of SC4A ($(0-5.5) \times 10^{-3}$ M, 5 ml) with excess cinchona alkaloids were stirred until equilibrium was achieved at pH 7.2 which was adjusted by 1.0 M NaOH. After removing the insoluble substance by centrifugation (10,000 rpm) twice for 10 min, the complexes were obtained by the method of freeze-drying. The residues were completely dissolved in D_2O . The concentrations of soluble drugs in the residues were measured by ^1H NMR and calculated using 2,2-dimethyl-2-silapentane-5-sulfonate as an external reference. ^1H NMR spectra were recorded with a Bruker AV 400 spectrometer (Bruker Corp., Germany).

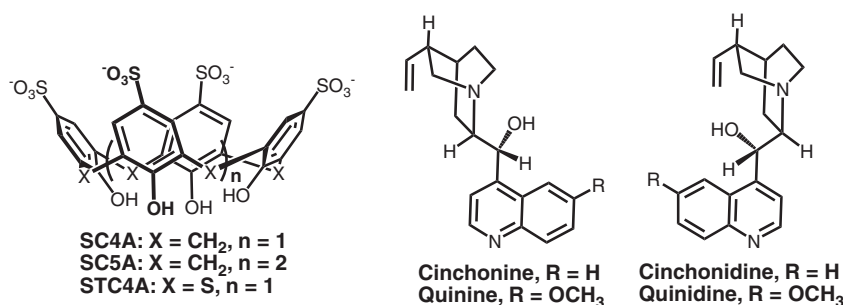
Mimic release of an SC4A + quinidine complex to a model micelle

The release was assessed by fluorescence spectroscopy. Sodium dodecyl sulfonate (SDS) was used as a model micelle system (22). Fluorescence spectra of quinidine (1.0×10^{-5} M) in pH 7.2 phosphate buffer solutions with SC4A (0 or 4.0×10^{-3} M) and SDS ($(0-4.0) \times 10^{-2}$ M) were measured at 25°C.

Results and discussion

Fluorescence spectral titrations

Four cinchona alkaloids employed, quinidine, quinine, cinchonine and cinchonidine, are strongly fluorescent. Their fluorescent is sensitive to environmental changes, which enable us to investigate the inclusion complexation with calixarenes by fluorescence spectroscopy. Three smaller host analogues (Scheme 1), SC4A, SC5A and STC4A, were selected for their relatively stable pre-organised cone shapes, while the other larger ones are always conformationally susceptible (7c). The fluor-



Scheme 1. Structures of three water-soluble calixarene hosts and four cinchona alkaloid guests.

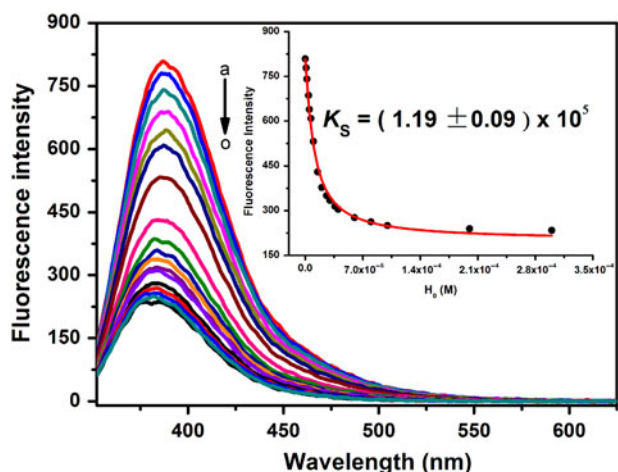


Figure 1. Fluorescence spectral changes of quinine (1.0×10^{-5} M) upon addition of SC4A (a \rightarrow o $0-3.0 \times 10^{-4}$ M) in pH 7.2 aqueous solution at 25°C and the nonlinear least-squares analysis (inset) of the fluorescence intensities used to calculate the complex stability constant (K_S).

Fluorescence spectral titrations were performed in both phosphate buffer and aqueous solutions to examine the effect of ionic strength on the binding ability. Furthermore, two pH values, 7.2 and 2.0, were employed to mimic different biological environments, serum and gastric acid, respectively. As a typical example, Figure 1 depicts the fluorescence quenching of quinine resulting from the complexation of SC4A in pH 7.2 aqueous solution. The emission intensity gradually decreases upon the stepwise addition of SC4A, mainly ascribed to the photoinduced electron transfer effect from electron-rich calixarene to quinoline. The fluorescence quenching indicates that quinine was captured into the SC4A cavity apart from bulk water. Similar results can be obtained for the other host-guest pairs at pH 7.2 and pH 2.0 in both phosphate buffer and aqueous solutions.

The stoichiometry for the inclusion complexation of calixarenes with cinchona alkaloids was determined by Job's experiments. Figure 2(a) shows the 1:1 stoichiometry for the inclusion complexation of SC4A with cinchonine at pH 7.2, and Figure 2(b) indicates the 1:1 inclusion complexation between SC5A and cinchonine at pH 2.0. The same results were obtained in the other host-guest cases.

Binding mode

The formation of inclusion complexes between calixarenes and cinchona alkaloids was validated by ^1H NMR spectroscopic experiments. As shown in Figure 3, upon addition of SC4A, the protons of cinchonidine exhibit a visible upfield shift owing to the ring current effect of the aromatic nuclei of calixarenes, which suggests that the cinchonidine guest is captured by the calixarene cavity.

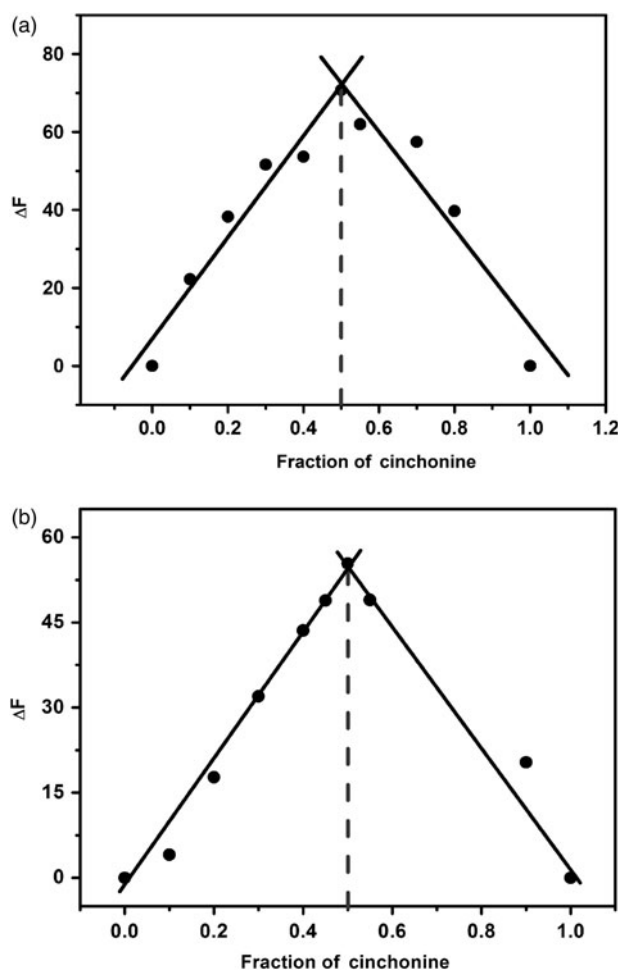


Figure 2. Job's plots of SC4A + cinchonine at pH 7.2 ($[\text{SC4A}] + [\text{cinchonine}] = 2.0 \times 10^{-5}$ M) and SC5A + cinchonine at pH 2.0 ($[\text{SC5A}] + [\text{cinchonine}] = 2.0 \times 10^{-5}$ M).

Notably, the binding mode at pH 7.2 is different from that at pH 2.0. Figure 3(a) shows that the aliphatic protons of cinchonidine underwent pronounced upfield shifts upon addition of SC4A at pH 7.2, while no appreciable shift was observed for the aromatic protons. Figure 3(b) shows that the aromatic protons of cinchonidine underwent upfield shifts at pH 2.0, while no appreciable shift was observed for the aliphatic protons. The ^1H NMR results display that the aliphatic portion of cinchonidine was preferentially embedded into the calixarene cavity at pH 7.2, whereas the aromatic portion of cinchonidine was preferentially embedded into the calixarene cavity at pH 2.0 (Scheme 2). The differential binding modes between pH 2.0 and pH 7.2 mainly originate from the protonation state of guest N atoms. At pH 2.0, both the aromatic and aliphatic N atoms are protonated, and calixarene prefers to encapsulate the aromatic quinolone. At pH 7.2, only the aliphatic N atom is protonated, and calixarene prefers the aliphatic portion. It should be mentioned that the complexation-induced

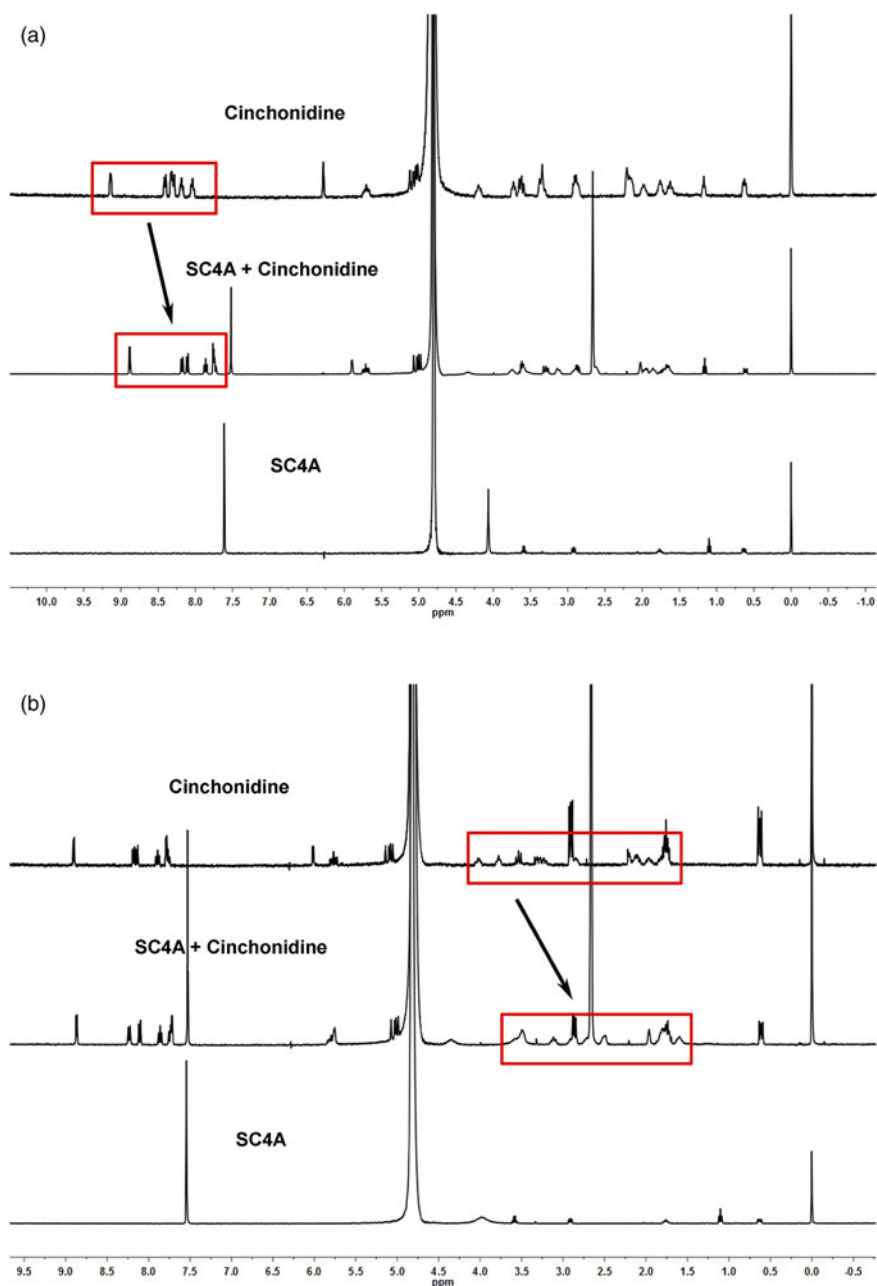


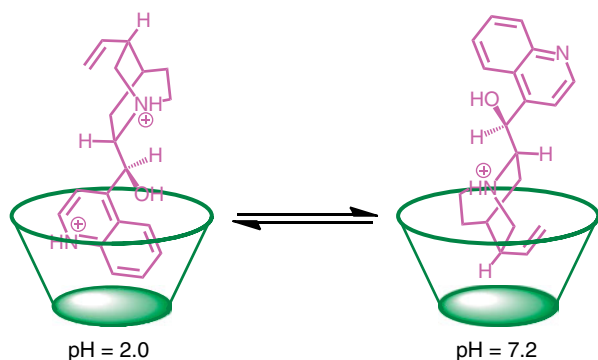
Figure 3. (Colour online) The ¹H NMR spectra of cinchonidine in the absence and presence of SC4A at pH 2.0 (a) and pH 7.2 (b).

shifts of cinchonidine protons by SC4A are not as large as those of classical guests reported before (23). One reasonable explanation is that the cinchonidine guest was immersed into the SC4A cavity relatively shallowly. In other words, cinchonidine is located closer to the rim sulfonates than the bottom of the binding pocket, mainly ascribing to the large guest size.

Binding stability

Using a nonlinear least squares curve-fitting method, we obtained the complex stability constant (K_S) for each

host–guest association. The K_S values obtained at pH 2.0 and pH 7.2 are listed in Table 1. It can be seen that all three calixarenes form stable (or at least modest) complexes with four cinchona alkaloids although the K_S values are affected by pH and ionic strength to some extent, which ensures calixarenes are potentially effective drug carriers for cinchona alkaloids. The host–guest complexes at pH 2.0 are more stable than those at pH 7.2 as a result of charge interaction. According to the dissociation constants (pK_a) of cinchona alkaloids (24), both the aromatic and aliphatic N atoms are protonated in an acidic environment



Scheme 2. (Colour online) The deduced binding modes of SC4A with cinchonidine according to ^1H NMR spectra.

(pH 2.0), while only the aliphatic N atom is protonated in a neutral environment (pH 7.2). It is easily acceptable that positive divalent guest molecule donates stronger charge interaction to negatively charged calixarene than positive monovalent guest molecule. The complex stability undergoes almost one order of magnitude decrease when the surroundings change from pH 2.0 to pH 7.2. This is somewhat indicative that cinchona alkaloids are inclined to be encapsulated in the calixarene cavity in the gastric acid environment and partially released in the serum environment.

On the other hand, the complexation between calixarenes and cinchona alkaloids is ionic strength-dependent. The K_S values in phosphate buffer are 1–2 orders of magnitude lower than those in aqueous solution, arising from the competitive binding of Na^+ with calixarenes (25) as well as the effect of ionic strength (26). Besides the intrinsic Na^+ (SCnAs are themselves a source of Na^+), SCnAs are also able to bind various metal cations with distinguishable affinities

(25a, 27). As a result, SCnAs show some potential as drug carriers with a cationic response. For example, the Na^+ and K^+ concentrations are much different inside and outside the cell ($[\text{Na}^+]_{\text{intra}} = 10 \text{ mM}$; $[\text{Na}^+]_{\text{extra}} = 145 \text{ mM}$; $[\text{K}^+]_{\text{intra}} = 150 \text{ mM}$; $[\text{K}^+]_{\text{extra}} = 5 \text{ mM}$). SCnAs exhibit stronger binding affinities to K^+ than Na^+ (25a). We are therefore convinced in theory that the controlled release of the loaded drug can be achieved by Na^+/K^+ ionic strength. Relative to K^+ , Na^+ is a weaker competitor to the calixarene + drug complex. Consequently, the complex is more stable in the extracellular environment than the intracellular environment. When the complex enters into cell, K^+ as a stronger competitor would trigger the drug release from the calixarene cavity. Herein, we would like to stress that it merely represents a proof-of-principle approach for controlled release based on competitive binding at the present stage, and its actual application *in vivo* should be practically difficult.

Among three water-soluble calixarenes employed, SC4A affords the strongest binding affinities to four cinchona alkaloids. The SC4A cavity appears bowl shaped, while the SC5A one appears more like a shallow dish (5e, 28). That is, the SC5A cavity is larger in diameter but shallower than the SC4A cavity, and therefore, in most cases, SC5A cannot capture guest molecules as tightly as SC4A (4). Compared with STC4A, SC4A possesses a more compact framework and higher π -electron density of the cavity (29), leading to more effective π -stacking interactions with guests and then forms more stable complexes with cinchona alkaloids. Moreover, the biocompatibility of SC4A has been comprehensively demonstrated. SC4A is therefore more suitable to act as drug carrier of cinchona alkaloids than the other two STC4A and SC5A. In the following solubilisation and mimic release experiments, we focus only on the SC4A system.

Table 1. Stability constants (K_S) for the inclusion complexation of SCnAs with cinchona alkaloids in phosphate buffer solution (PBS) and in aqueous solution (aq) at 25°C.

| | Cinchonine | Cinchonidine | Quinine | Quinidine | |
|--------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----|
| pH 2.0 | | | | | |
| SC4A | $(7.4 \pm 0.4) \times 10^5$ | $(1.6 \pm 0.1) \times 10^6$ | $(2.1 \pm 0.1) \times 10^5$ | $(3.2 \pm 0.3) \times 10^5$ | aq |
| | $(7.1 \pm 0.2) \times 10^4$ | $(8.2 \pm 0.3) \times 10^4$ | $(2.3 \pm 0.1) \times 10^4$ | $(2.5 \pm 0.1) \times 10^4$ | PBS |
| SC5A | $(7.9 \pm 0.3) \times 10^4$ | $(7.4 \pm 0.2) \times 10^5$ | $(6.5 \pm 0.1) \times 10^4$ | $(5.5 \pm 0.7) \times 10^4$ | aq |
| | $(3.1 \pm 0.2) \times 10^4$ | $(2.3 \pm 0.1) \times 10^4$ | $(1.2 \pm 0.1) \times 10^4$ | $(1.3 \pm 0.1) \times 10^4$ | PBS |
| STC4A | $(2.7 \pm 0.4) \times 10^5$ | $(7.5 \pm 0.2) \times 10^5$ | $(2.8 \pm 0.1) \times 10^5$ | $(1.5 \pm 0.3) \times 10^5$ | aq |
| | $(3.1 \pm 0.2) \times 10^4$ | $(1.4 \pm 0.1) \times 10^4$ | $(1.9 \pm 0.1) \times 10^4$ | $(2.5 \pm 0.3) \times 10^4$ | PBS |
| pH 7.2 | | | | | |
| SC4A | $(9.8 \pm 0.6) \times 10^4$ | $(1.3 \pm 0.1) \times 10^5$ | $(1.2 \pm 0.1) \times 10^5$ | $(1.1 \pm 0.1) \times 10^5$ | aq |
| | $(2.0 \pm 0.1) \times 10^3$ | $(4.1 \pm 0.2) \times 10^3$ | $(2.0 \pm 0.2) \times 10^3$ | $(3.8 \pm 0.2) \times 10^3$ | PBS |
| SC5A | $(5.5 \pm 0.3) \times 10^4$ | $(6.0 \pm 0.4) \times 10^4$ | $(5.8 \pm 0.2) \times 10^4$ | $(5.9 \pm 0.3) \times 10^4$ | aq |
| | $(2.6 \pm 0.1) \times 10^3$ | $(3.1 \pm 0.4) \times 10^3$ | $(4.5 \pm 0.2) \times 10^3$ | $(3.6 \pm 0.2) \times 10^3$ | PBS |
| STC4A | $(4.2 \pm 0.6) \times 10^4$ | $(2.6 \pm 0.2) \times 10^4$ | $(2.9 \pm 0.2) \times 10^4$ | $(2.2 \pm 0.1) \times 10^4$ | aq |
| | $(4.3 \pm 0.3) \times 10^3$ | $(7.4 \pm 0.5) \times 10^3$ | $(6.6 \pm 0.3) \times 10^3$ | $(2.4 \pm 0.3) \times 10^3$ | PBS |

Solubilisation

Drug solubilisation by SCnAs in aqueous media has been achieved for several insoluble drugs (12a, 13). In order to evaluate the capability of SCnAs as carriers for cinchona alkaloids, we tested the ability of SC4A to enhance the solubility of quinidine and cinchonine. Phase solubility profiles (30) measured at 25°C and pH 7.2 of the amount of cinchona alkaloids solubilised versus the concentration of SC4A are shown in Figure 4. The water solubility of quinidine and cinchonine improved significantly with increasing concentration of SC4A. For example, the solubility of cinchonine increases from 6.8×10^{-5} M to 1.1×10^{-3} M owing to the complexation of SC4A. The excellent solubility enhancements achieved by SC4A suggest a bright applicability of SCnAs in drug solubilisation and delivery of cinchona alkaloids.

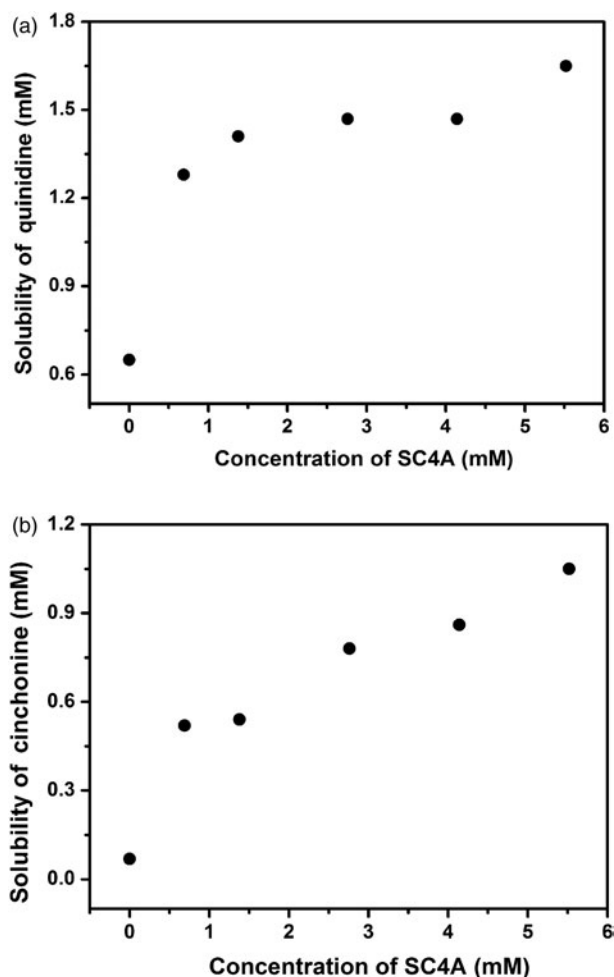


Figure 4. Phase solubility diagrams measured in the presence of increasing concentrations of SC4A ($(0-5.5) \times 10^{-3}$ M) at pH 7.2: (a) quinidine (b) cinchonine.

Mimic release of SC4A + quinidine complex to a model micelle

To be qualified drug carriers, except for providing a high level of stabilisation of cinchona alkaloids, SCnAs must demonstrate the capability of releasing the complexed cinchona alkaloids when the surroundings change (22). The guest release of the SC4A + quinidine complex in the presence of micelles is assessed by fluorescence spectroscopy based on the fact that the fluorescence intensities of cinchona alkaloids are sensitive to the polarity of the solvent/environment and the negatively charged micelles used as the competitive receptors have a negligible level of fluorescence. Because we have already discussed the fluorescence quenching of cinchona alkaloids upon complexation of SCnAs, fluorescence spectra of quinidine and SC4A + quinidine in the presence of SDS micelles were investigated as shown in Figure 5. It illustrates that the emission behaviours of free

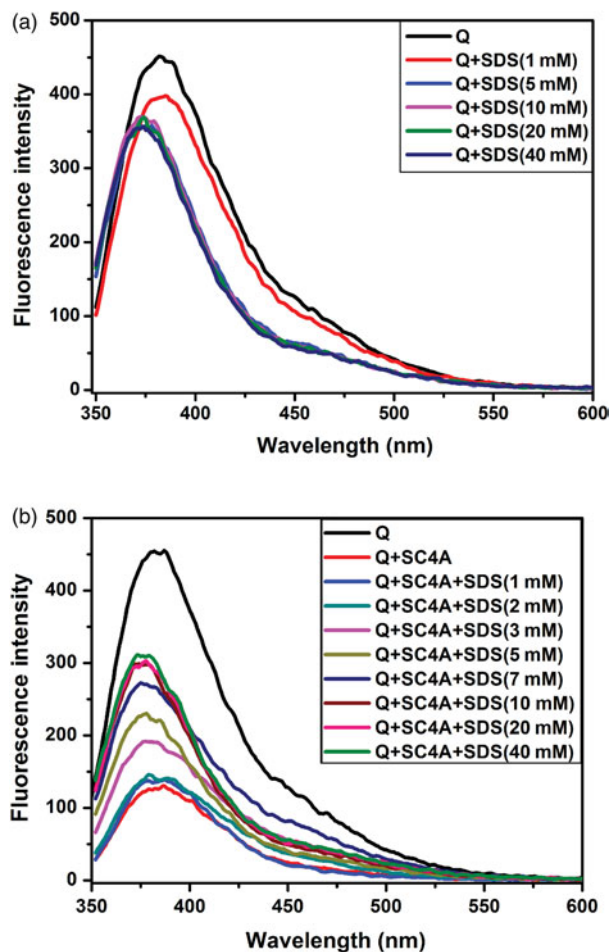


Figure 5. (Colour online) Fluorescence spectral changes of quinidine (1.0×10^{-5} M) in the absence (a) or presence (b) of SC4A (4.0×10^{-3} M) upon addition of SDS ($(0-4.0) \times 10^{-2}$ M) at 25°C in phosphate buffer solution, pH 7.2. Phosphate buffer solution was employed to imitate *in vivo* environment.

quinidine and the SC4A + quinidine complex are noticeably altered in the presence of SDS micelles. In Figure 5(a), the fluorescence intensity of quinidine gradually decreases upon the stepwise addition of SDS until essentially unchanged above the critical micelle concentration of SDS. This phenomenon may attribute to the interaction between the cationic amine of quinidine and the sulfonic acid root of SDS. After the formation of micelles, this interaction reaches equilibrium. The fluorescence intensity of the SC4A + quinidine complex increases with enhancing concentration of SDS and finally achieves equilibrium when micelles are formed (Figure 5(b)). It indicates that quinidine has been released from the cavity of SC4A and possibly delivered to the surface of SDS micelles as a result of charge interactions. The fluorescence intensity does not recover to the maximum of free quinidine, possibly owing to the interaction between SDS and quinidine demonstrated above.

Conclusion

In summary, the inclusion behaviours of SCnAs with cinchona alkaloids were examined at pH 7.2 and pH 2.0 both in phosphate buffer and aqueous solutions, respectively. The fluorescence strengths of cinchona alkaloids were traced to determine the host-guest binding stabilities, where the fluorescence was quenched upon addition of calixarenes as a result of photoinduced electron transfer. SCnAs have shown strong binding abilities towards cinchona alkaloids, especially in acidic aqueous condition. Among three hosts, SC4A affords the strongest binding stabilities owing to the preorganised bowl shape and high π -electron density. Furthermore, desired solubility enhancement of quinidine was achieved by the complexation of SC4A. A certain degree of fluorescence recovery in the presence of SDS micelles indicates the release of cinchona alkaloids from the calixarene cavity. Consequently, the water-soluble sulfonatocalixarenes have been demonstrated as potential drug carriers for cinchona alkaloids.

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