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ORIGINAL ARTICLE

Highly effective binding and inverse fluorescent behavior of palmatine and *l*-tetrahydropalmatine alkaloids by *p*-sulfonatocalixarenes

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Abstract The complexation behavior of palmatine (P) and *l*-tetrahydropalmatine (*l*-THP) alkaloid guest molecules by *p*-sulfonatocalix[n]arene (SCnA, $n = 4,6,8$) hosts have been investigated by means of fluorescence spectra. It's found that P and *l*-THP alkaloids exhibit inverse fluorescent behavior upon the complexation with SCAs, i.e., fluorescence enhancement for P, and fluorescence quenching for *l*-THP. The complex stability constants decrease in the order of SC8A > SC6A > SC4A for each alkaloid. Particularly, SC8A displays extraordinarily strong binding abilities ($K_S = 46900 \pm 200\ M^{-1}$ for P and $104000 \pm 1000\ M^{-1}$ for *l*-THP).

Keywords Fluorescent behavior · Molecular recognition · Calixarenes · Palmatine · *l*-Tetrahydropalmatine

Introduction

Palmatine (P) and *l*-tetrahydropalmatine (*l*-THP) are clinically important natural alkaloids, and they exhibit a wide range of biochemical and pharmacological effects [1–4]. P possesses antimicrobial, antimalarial, anti-inflammatory, antipyretic, hepatoprotective and vasodilatory activities [1–9], and *l*-THP possesses analgesic, hypnotic, hypotensive and anti-arrhythmia effects and inhibiting thrombocyte aggregation [1–4, 10–13]. In addition, they have been shown to display significant antitumor activities [14–17]. Recently, P and *l*-THP alkaloids have also been demonstrated to be capable of forming complexes with DNA, RNA and proteins [18–27]. For example, P can intercalate into doublestranded DNA, perturb the structure of DNA, and hinder or to suppress the normal physiological functions of DNA [28–31]. Moreover, P can be used as the fluorescent sensors for DNA and proteins [32, 33].

p-Sulfonatocalix[n]arenes (SCnA, $n = 4,5,6,8$) have been a significant class of supramolecular hosts [34–39]. They are highly soluble in water [40], less toxic [41, 42] and possess broad applications in the biological area, such as the artificial signaling acetylcholine receptors, indicator of ion channels, metalloenzyme models, anti-viral agents and thrombosis [43–45]. In the present work, we wish to report the binding behavior of P and *l*-THP alkaloids by SCAs using fluorescence spectra (Chart 1). Our interest is not only to elucidate the highly effective binding abilities between hosts and guests, but also to examine the inverse complexation-induced fluorescence changes. Through the present studies of host-guest recognition and fluorescent sensor behavior, the applications of P and *l*-THP alkaloids will be broadened, and even be given new characteristics and significations.

Experimental

General

Fluorescence spectra were measured using a Shimadzu spectrofluorometer model FP-5301PC using a conventional $10 \times 10 \times 45\ mm^3$ quartz cell. The fluorescence experiments were kept at a constant temperature of 25°C through a Shimadzu TB-85 Thermo Bath unit. The excitation wavelengths for P and *l*-THP were 347 and 282 nm.

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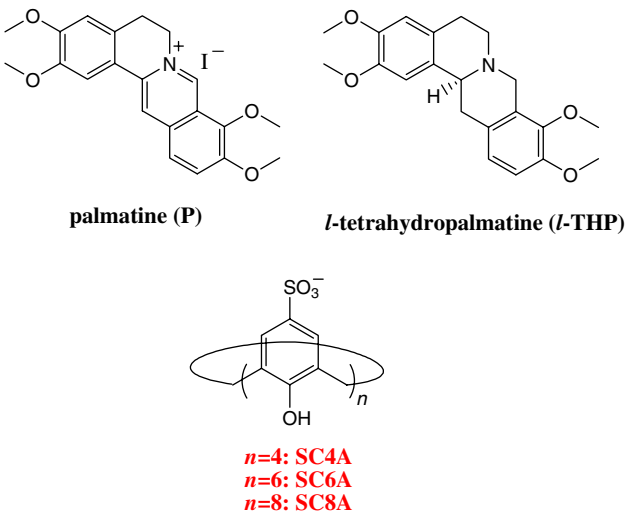

Chart 1 Structural formulas of SCA host and alkaloid guest molecules

Materials

The two isoquinoline alkaloid guests, i.e., palmatine (P) and *l*-tetrahydropalmatine (*l*-THP), were commercially available and used without further purification. *p*-Sulfonatocalixarenes (SCAs) {i.e., *p*-sulfonatocalixarene tetrasodium (SC4A), *p*-sulfonatocalixarene hexasodium (SC6A) and *p*-sulfonatocalixarene octasodium (SC8A)} were prepared simply by the direct reaction of (*p*-tert-Butyl- or H–) calixarenes with conc. H_2SO_4, followed by treating with inorganic salts [46–49]. All other chemicals were commercially available and used without further purification, except otherwise noted. The phosphate buffer solution of pH 2.0 was prepared by dissolving sodium dihydrogen phosphate in distilled, deionized water to make a 0.1 mol dm^{-3} solution, which was then adjusted to pH 2.0 by phosphoric acid. The phosphate buffer solution of pH 7.2 was prepared by dissolving disodium hydrogen phosphate (25.79 g) and sodium dihydrogen phosphate (4.37 g) in distilled, deionized water (1000 ml) to make a 0.1 mol dm^{-3} solution.

Results and discussion

Spectral titrations

Spectral titrations of the three SCAs with P and *l*-THP were performed at 298.15 K in a phosphate buffer solution of pH 2.0, to quantitatively assess the inclusion complexation behavior of these compounds. The spectral changes depended critically on the formation of a new species, that is, a host-guest complex, showing the spectral enhancement or quenching. As shown in Fig. 1, the fluorescence

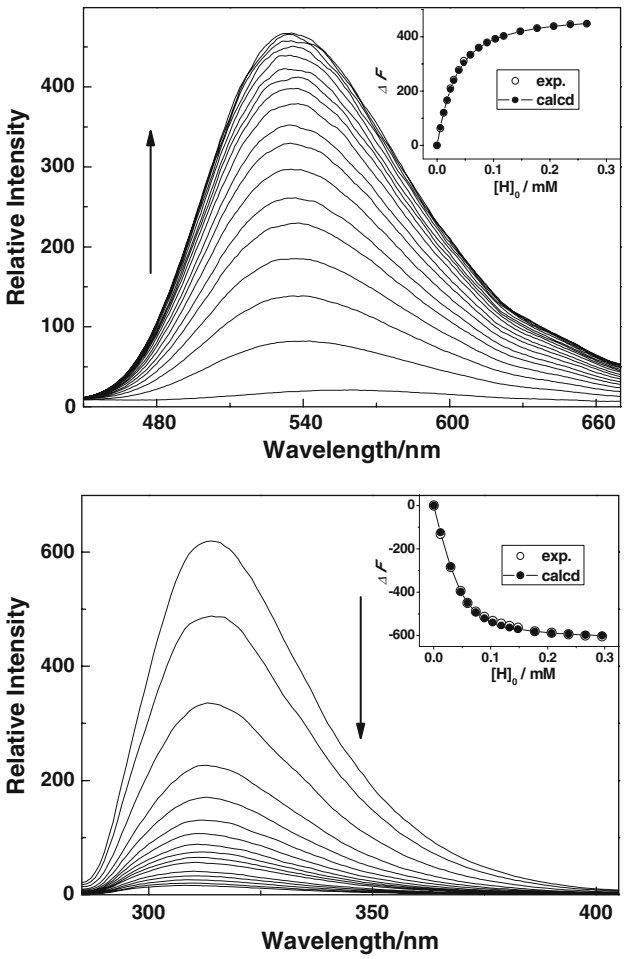

Fig. 1 Fluorescence spectra of P(upper) and *l*-THP (lower) in the presence and absence of SC8A in aqueous phosphate buffer solution (pH 2.0) at 298.15 K. Inset: the nonlinear least-squares analysis of the differential intensity (ΔF) to calculate the complex stability constant (K_S). The concentrations of P and *l*-THP are 1.88×10^{-5} and 4.79×10^{-5} mol dm^{-3}, respectively

intensity of P and *l*-THP gradually changed with the addition of SC8A. However, in the control experiments, under identical conditions the fluorescence intensities of the guests were not appreciably affected by the addition of 4-phenolsulfonate, i.e., the monomeric unit of SCAs. These phenomena indicated that the guests must be included into the cavities of the host, forming the host-guest inclusion complexes. The similar results are also observed in the spectral titrations of the guests with SC4A and SC6A. Assuming 1:1 inclusion complexation stoichiometry between the three SCAs and the two alkaloids, the complex stability constants (K_S) could be calculated by analyzing the sequential changes in fluorescence intensity (ΔF) of guest that occurred with changes in host concentration. This analysis was carried out by using a nonlinear least-squares curve-fitting method. For each alkaloid guest examined, the plot of ΔF as a function of $[H]_0$ gave an excellent fit

Table 1 Complex stability constants (K_S/M^{-1}) and Gibbs free energy changes ($-\Delta G°/kJ\ mol^{-1}$) for 1:1 intermolecular complexation of P and *l*-THP with SCAs in phosphate buffer solution (pH 2.0) at 298.15 K

	P		*l*-THP	
	K_S	$-\Delta G°$	K_S	$-\Delta G°$
SC4A	783 ± 10	16.52	8180 ± 50	22.33
SC6A	3640 ± 40	20.33	16500 ± 200	24.07
SC8A	46900 ± 200	26.66	104000 ± 1000	28.64

($R > 0.99$), verifying the validity of the 1:1 inclusion complexation stoichiometry assumed. Additionally, the 1:1 inclusion complexation stoichiometry had also been proved by the job's experiments. In the repeated measurements, the K_S values were reproducible within an error of ±5%. The complex stability constants (K_S) obtained for all of the host-guest combinations are listed in Table 1, along with the free energy changes ($-\Delta G°$).

Fluorescence sensing

Molecular sensing based on the guest involved response of the receptor is a very significant topic in organic chemistry. Herein, fluorescence spectra of P and *l*-THP alkaloids with the three SCA hosts were performed at 298.15 K in a phosphate buffer solution of pH 2.0. As shown in Fig. 2, fluorescence of P and *l*-THP significantly changed upon the addition of SCAs. However, in the control experiments, under identical conditions the fluorescence intensities of the guests were not appreciably affected by the addition of 4-phenolsulfonate, i.e., the monomeric unit of SCAs. These phenomena indicated that the guests must be included into the cavities of the hosts, forming the host-guest inclusion complexes.

The fluorescence intensity of P ($\Phi_P = 0.0046$) showed a steep increase accompanied with the visible hypsochromic shift in the presence of the three SCAs. And the order of the fluorescence intensity changes was consistent with the number of phenolic units in the calixarenes, i.e., SC8A > SC6A > SC4A ($\Phi = 0.0241$, 0.0146 and 0.0144 for SC8A, SC6A and SC4A), which was the same as the order of hypsochromic/blue shifts (25, 24, and 17 nm for SC8A, SC6A and SC4A) (Table 2). Generally, the fluorescence intensity of P is sensitive to change in its microenvironment. That is, it barely fluoresces in a hydrophilic microenvironment but emits strong fluorescence in a highly hydrophobic one. The P alkaloid molecule must insert into the hydrophobic cavity of the SCAs, and the resulting decrease of polar microenvironment led to the hypsochromic/blue shift and the fluorescence enhancement. Herein, the intensity of the emittance is strong enough to be readily

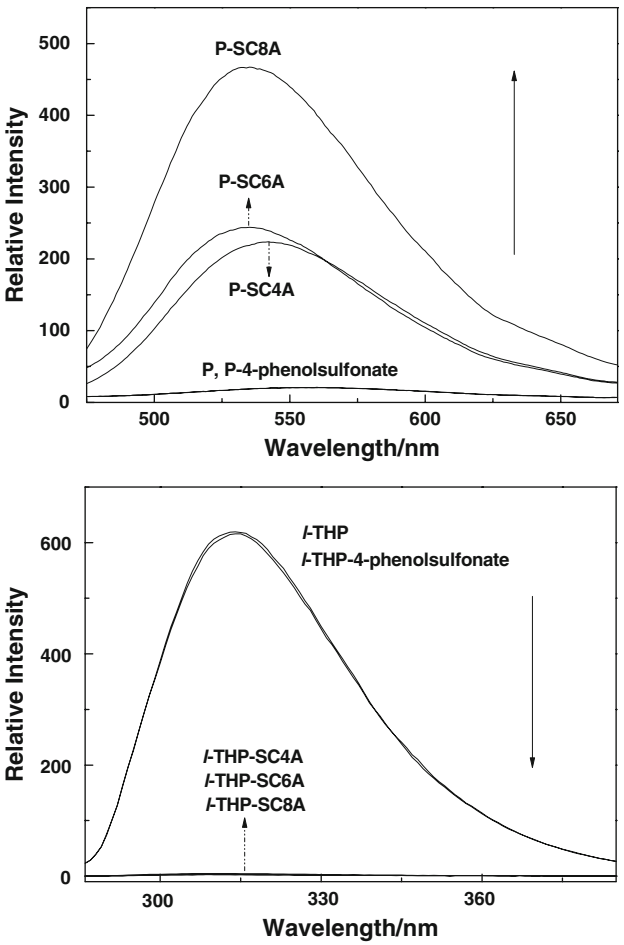

Fig. 2 Fluorescence spectra of P (upper) and *l*-THP (lower) in the presence and absence of SCAs and 4-phenolsulfonate in aqueous phosphate buffer solution (pH 2.0) at 298.15 K. The concentrations of P and *l*-THP are 1.88×10^{-5} and 4.79×10^{-5} mol dm^{-3}

Table 2 Hypsochromic/Blue shifts of P and *l*-THP alkaloids in the presence of SCAs in phosphate buffer solution (pH 2.0) at 298.15 K

	SC4A	SC6A	SC8A
P	17(559 → 542)	24(559 → 535)	25(559 → 534)
l-THP	3(314 → 311)	4(314 → 310)	6(314 → 308)

distinguished by the naked eye with a UV lamp (Fig. 3). It's well known that isoquinoline alkaloids are potential photoanticipins (phototoxins [50–52]), since they can initiate the formation of singlet oxygen ($^1O_2$) and the oxidation of biological substrates. However, isoquinoline alkaloids always exhibit low quantum yields for fluorescence (Φ). Therefore, the present large enhancement of the Φ value of P can help improve its application as photoanticipins (Table 3).

Significantly different with P, for the *l*-THP alkaloid, the fluorescence intensity decreased drastically upon the addition of SCAs. In addition, the complexation-induced

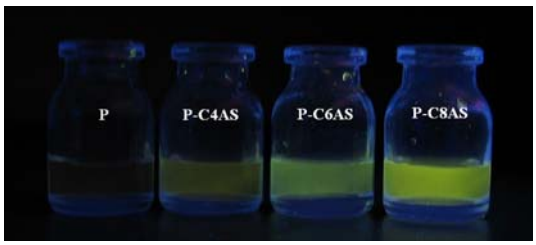

Fig. 3 Visible emission observed from samples of P and SCAs. Left to right: no host, P + SC4A, P + SC6A and P + SC8A

Table 3 Fluorescence quantum yields (Φ) of P, *l*-THP and their complexes in phosphate buffer solution (pH 2.0) at 298.15 K

	Guest	Complexes		
		SC4A	SC6A	SC8A
P	0.0046	0.0144	0.0146	0.0241
l-THP	0.0991	0.0072	0.0067	0.0065

blue shifts of *l*-THP were not as marked as that of P, since only 3 ~ 6 nm were observed. Although all the three SCAs can drastically quench the fluorescence of *l*-THP, SC8A displays the strongest quenching ability, because only 6 mol equivalents of SC8A (2.95×10^{-4} mol dm^{-3}) can effectively quench the *l*-THP (4.79×10^{-5} mol dm^{-3}) fluorescence ($\Phi_{l\text{-THP}} = 0.0991$; $\Phi_{l\text{-THP-SC8A}} = 0.0065$). The decreases in fluorescence intensity of *l*-THP in the presence of SCAs are mainly attributed to the inclusion complexation, not just to the simple quenching effect of sulfonate groups [53–55]. The quenching phenomena can be rantionlized in terms of efficient quenching through hydrogen atom abstraction from the phenolic hydroxyl groups and possibly, also exciplex formation with the aryl rings, which is a composite effect [56]. For both alkaloid guests, the SC8A-complexation induced fluorescence changes (intensities and blue shifts) are much remarkable. This fluorescent behavior provides advantageous evidence that SC8A form more strongly stable inclusion complex with these two alkaloids, a conclusion which is also supported by the complex stability constants (see Table 1).

We also examined the fluorescent behavior of P and *l*-THP with SC8A in a phosphate buffer solution of pH 7.2. For P alkaloid, the similar fluorescence enhancement and hypsochromic/blue shift were found. However, compared with pH 2.0, the fluorescence intensity of P-SC8A complex decreased ($\Phi = 0.0241$ at pH 2.0 $\rightarrow$ 0.0106 at pH 7.2). At pH 2.0, eight phenolic hydroxyl groups in SC8A are all protonated, while two of them lose at pH 7.2 [57]. Therefore, the decrease of fluorescence intensity (P-SC8A complex) at pH 7.2 should be due to the enhanced electron transfer from the host to the excited P alkaloid since the phenolates can be oxidized easier than the corresponding phenols. *l*-THP wasn't soluble in neutral water, so fluorescence spectra of this alkaloid with SCA hosts were not performed in the pH 7.2 buffer solution.

Molecular binding ability

At the present pH value (2.0), both P and *l*-THP are protonated. It is well documented that the electrostatic, hydrogen bond, π–π, C–H$\cdots\pi$ and van der Waals interactions may play crucial role in the complexation of SCAs with cationic guests. Since these interactions are closely related to the distance and contacting surface area between host and guest, a good host-guest induced-fit may dominate the stability of the complex formed between SCAs and the guests. Additionally, the conformation change of SCAs, closely related with the flexibility, is also an important factor in the host-guest complexation [58]. The previous works show that, for the smaller guests (e.g. pyridine derivatives), the SCA with smaller ring size always shows stronger binding abilities [59, 60]; while for the larger guests (e.g. dye molecules), the SCA with larger ring size shows stronger binding abilities [53–55, 61, 62]. According to this concept, SC8A should give enhanced binding abilities toward P and *l*-THP than SC4A and SC6A because of its high flexibility and its comparable size to the two alkaloid guests. In the three SCAs mentioned here, SC8A provides the largest complexation stability constants with P (46900 ± 200 M^{-1}) and *l*-THP (104000 ± 1000 M^{-1}). The complexation stability constants monotonically increase with the number of phenolic units in the calixarenes, SC4A < SC6A < SC8A, for each alkaloid guest compounds. The ratios of complex stability constants (K_S) of SC4A, SC6A and SC8A with alkaloid guest molecules are 1:4.6:59.9 for P and 1:2.0:12.7 for *l*-THP. With a same SCA, the alkaloid guest displays the same K_S order, i.e., *l*-THP > P. It's interesting to be pointed that although SC4A shows the weakest binding abilities ($K_S = 783$ M^{-1} for P and 8180 M^{-1} for *l*-THP), it provides the largest K_S ratio (*l*-THP/P) of 10.4:1. That is to say, the ratio of K_S (*l*-THP/P) decreases with the number of phenolic units in the calixarenes (10.4:1, 4.5:1 and 2.2:1 for SC4A, SC6A and SC8A, respectively), which is just contrary to the binding abilities.

Conclusion

We report the strong binding abilities and fluorescence sensor behavior of P and *l*-THP alkaloids by SCAs. For each alkaloid guest, the complexation stability constants monotonically increase with the number of phenolic units in the calixarenes, SC4A < SC6A < SC8A. The two alkaloid guests exhibit inverse fluorescent behavior upon the complexation with SCAs, i.e., fluorescence enhancement for P,

and fluorescence quenching for *l*-THP. The effective complexation-induced fluorescence sensor behavior of the two alkaloids can help improve their applications in bioorganic and medical chemistry. In particular, the large enhancement of the Φ value of P in the presence of SCAs could make it possess the potential to serve as photoanticipins. Endeavors to explore the applications of alkaloid-SCA complexes are currently in progress.

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