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CHARACTERIZATION OF THREE-DIMENSIONALLY EXTENDED HYDROPHOBIC CAVITIES. DIFFERENCE IN MOLECULAR RECOGNITION ABILITY BETWEEN STEROID AND OCTOPUS CYCLOPHANES

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The guest-binding behavior of two different cyclophane hosts, each being capable of providing a three-dimensionally extended hydrophobic cavity toward aromatic guests, was examined in aqueous media: a steroid cyclophane bearing four rigid cholate moieties and an octopus cyclophane having four flexible double-chain segments. Even though the binding constant for 2,7-dihydroxynaphthalene with the steroid cyclophane was comparable to that with the octopus cyclophane, the guest binding modes were very different from each other, as confirmed by ^{1}H NMR spectroscopy. That is, the steroid cyclophane incorporates the guest into its rigid macrocyclic cavity with axial geometry whereas the octopus cyclophane provides a three-dimensional space created by the macrocyclic skeleton and the flexible hydrocarbon chains so that the long axis of the guest becomes more or less perpendicular to the molecular axis of the host upon complexation. Temperature-dependent molecular recognition by these hosts toward 8-anilinonaphthalene-1-sulfonate was examined by means of fluorescence spectroscopy. Characteristic differences in the guest-binding mode between these hosts were sensitively reflected in the thermodynamic entropy change on host–guest complexation and the temperature-dependent microscopic viscosity experienced by the guest at the binding site. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Bioactive molecules such as antibodies, enzymes, nucleic acids and receptors exhibit supramolecular functions originating from ingenious molecular recognition that is attained by integration of various non-covalent interactions. Recent tremendous advances in supramolecular chemistry have deepened our understanding of non-covalent interactions for molecular recognition and have resulted in many artificial supramolecules.[1–6] As one type of such supramolecular elements, cyclophanes capable of furnishing a large hydrophobic cavity have been widely employed up to the present time.[7–15] Although simple cyclophane derivatives exhibit valuable biomimetic functions when they constitute supramolecules, the supramolecular effects could be made more pronounced by modifications of their shallow cavities to afford three-dimensionally extended hydrophobic spaces. Among various cyclophane-type macrocyclic hosts, so-called cage-type cyclophanes have been developed along this line.[16–22]

On the other hand, we have also adopted another approach to create three-dimensionally extended hydrophobic spaces by the introduction of multiple hydrophobic branches into the cyclophane skeleton. We call cyclophane derivatives having four rigid bile acid moieties 'steroid cyclophanes'[23–27] and cyclophanes bearing eight flexible hydrocarbon chains 'octopus cyclophanes.'[24,28–30] In aqueous media, the hydrophobic branches of the host molecule come close to each other through the hydrophobic interaction to furnish a large cavity for molecular recognition. We have already clarified that steroid cyclophanes perform effective guest recognition as artificial cell-surface receptors embedded in bilayer membranes[23–27] and that the octopus cyclophanes behave as potent artificial apoenzymes for the catalytic simulation of vitamin B_6- and B_{12}-dependent enzymes.[31,32]

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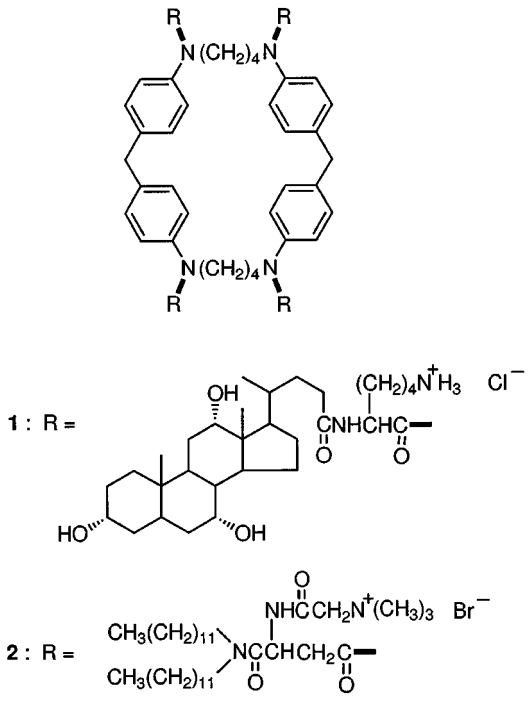
In order to obtain further insights into the molecular recognition abilities of cyclophanes bearing multiple hydrophobic branches, we have now examined differences in guest binding behavior in aqueous solutions between the steroid cyclophane **1** and octopus cyclophane **2** with the focus on their guest-binding modes and temperature-dependent complexation behavior.

EXPERIMENTAL

Materials. 2,7-Dihydroxynaphthalene (2,7-DHN) (Wako Pure Chemical Industries, Osaka, Japan) and sodium 8-anilinonaphthalene-1-sulfonate (ANS) (Nacalai Tesque, Kyoto Japan) were guaranteed reagents and used without further purification. A steroid cyclophane, 1, 6, 20, 25-tetrakis {[2 - (3α, 7α, 12α - trihydroxy-5β-cholan-24-oyl)amino]-6-ammoniohexanoyl}-1, 6, 20, 25-tetraaza-[6.1.6.1]paracyclophane tetrachloride (**1**)[25] and an octopus cyclophane, *N*, *N*′, *N*″, *N*‴-tetrakis {3-(*N*,*N*-didocecylcarbamoyl) - 3 - [(trimethylammonio)acetamido]propanoyl}-1, 6, 20, 25-tetraaza[6.1.6.1]paracyclophane tetrabromide (**2**),[24] were prepared according to literature methods.

Measurements. Surface tension measurements were performed with a Shimadzu ST-1 surface tensometer assembled according to the Wilhelmy principle and dynamic light-scattering measurements were carried out with a Photal (Otsuka Electronics) DLS-700 dynamic light-scattering spectrophotometer (He–Ne laser, 632·8 nm) equipped with a NEC PC-9801 RA personal computer. NMR spectra were taken on a JEOL JNM-270 spectrometer. Fluorescence spectra were measured with a Hitachi 650-40 spectrofluorimeter. Steady-state fluorescence polarization data were obtained on a Union Giken FS-501A spectrophotometer equipped with a Sord M200 Mark II microcomputer, and fluorescence lifetimes were recorded on a Horiba NAES-1100 time-resolved spectrofluorimeter.



Formulae 1 and 2.

RESULTS AND DISCUSSION

1,6,20,25-Tetraaza[6.1.6.1]paracyclophane (CP44), designed by Odashima *et al*.,[33] is one of the most effective macrocycles capable of binding aromatic guest molecules to its inner cavity. We adopted this molecular component here as a common macrocyclic skeleton for designing the steroid cyclophane **1** and the octopus cyclophane **2**. Thus, we could examine the molecular recognition abilities of the present hosts bearing multiple hydrophobic branches in comparison with that of CP44 itself.

Both cyclophanes **1** and **2** have an amphiphilic character capable of forming a molecular assembly in aqueous media. The critical aggregate concentration (cac) values in aqueous acetate buffer (0·01 mol dm^{-3}) at pH 5·0 and room temperature (298 K), as evaluated by means of surface tension measurements based on the Wilhelmy principle, were $6{\cdot}2\times10^{-6}$ and $6{\cdot}0\times10^{-4}$ mol dm^{-3} for **1** and **2**, respectively. Although the aggregate structures of these cyclophanes have not been clarified, the formation of relatively large aggregates was observed in a concentration range above the cac; the hydrodynamic diameters for aggregates of **1** and **2** in aqueous acetate buffer (0·01 mol dm^{-3}) at pH 5·0 and room temperature (298 K) were 650 and 580 nm, respectively, as evaluated by means of dynamic light-scattering measurements. In spite of such complexity in aggregation behavior, these cyclophanes showed simple guest-binding behavior based on 1:1 host–guest complexation regardless of the concentration range, above or below the cac (see below). Other macrocyclic molecules having amphiphilic character were found to incorporate a guest molecule into their cavities in 1:1 stoichiometry and such binding behavior was maintained in a similar manner even under conditions that allow aggregation of the host.[30,34,35]

First, we investigated the geometries of host–guest complexes of the cyclophanes with 2,7-dihydroxynaphthalene (2,7-DHN) in aqueous solution by means of ^{1}H NMR spectroscopy. Upon complexation of the guest with the steroid cyclophane at pD 5·0 and 303 K under conditions that allow the host to behave as a tetracationic species, **1** acted to induce marked upfield shifts of the proton signals of the guest while the signal splitting for aromatic protons of the host was much enhanced (Figure 1). The present spectral behavior is analogous to that reported for a complex

composed of CP44 and 2,7-DHN,[36] except for the following aspects. The aromatic proton signals of the steroid cyclophane are broader than those of CP44 in the presence and absence of the guest molecule, reflecting restricted molecular motion of the benzene rings in the former host due to presence of the hydrophobic branches. The extents of upfield shifts of the guest signals are 1-H≈4-H>3-H for the steroid cyclophane and 1-H>4-H>3-H for CP44.

For complexation of 2,7-DHN with the octopus cyclophane **2** at 303 K in D_2O, the ^{1}H NMR signals were very broad and the chemical shifts for the guest protons were not clearly observed. Such signal broadening was improved at higher temperatures. Hence the measurements were also carried out at 343 K for the steroid and octopus cyclophanes.

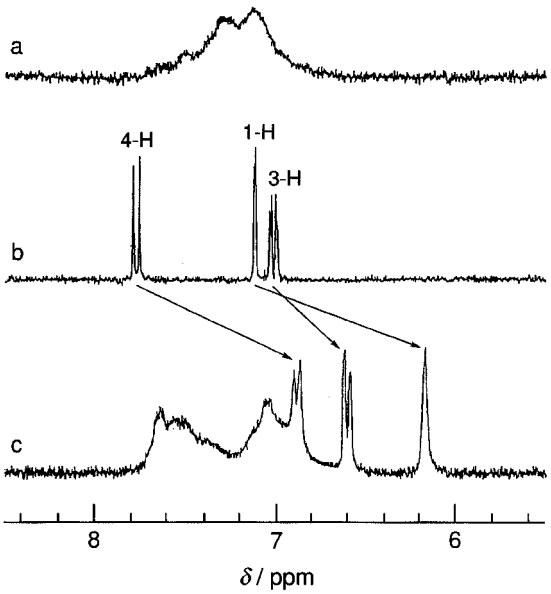


Figure 1. ^{1}H NMR spectra (270 MHz) of (a) **1** ($1{\cdot}0\times10^{-3}$ mol dm^{-3}), (b) 2,7-DHN ($1{\cdot}0\times10^{-3}$ mol dm^{-3}) and (c) **1** and 2,7-DHN ($1{\cdot}0\times10^{-3}$ mol dm^{-3} each) in D_2O at pH 5·0 and 303 K, with methanol (0·1% v/v) as an internal reference (δ=3·34 ppm)

Binding constants (K) for the host–guest complexes, free energies of complexation ($\Delta G°$) and complexation-induced shifts (CIS), the shifts of NMR signals for the guest upon 100% complexation, were evaluated from the ^{1}H NMR titration curves by means of the numerical curve-fitting method in a manner similar to that reported previously.[37] The results are summarized in Table 1 along with the corresponding values for a cyclophane derivative bearing four hydrophilic branches (**3**)[38] as a reference, **3** being present in a zwitterionic form at pD 6·5.

Whereas the binding of 2,7-DHN to the cyclophane was much enhanced by hydrophobic modification of the host molecule, the K values for the steroid cyclophane and the octopus cyclophane were comparable to each other at 343 K. However, the guest-binding modes of these cyclophane hosts were found to be markedly different from each other.

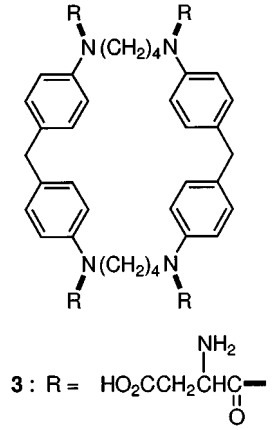
Judging from the CIS values, the guest is incorporated into the macrocyclic cavity with the long axis of the naphthalene ring parallel to the molecular axis of the steroid cyclophane, i.e. axial geometry, as shown schematically in Figure 2(a). The guest-binding mode of the steroid cyclophane is similar to that of **3**. It has been reported that the geometry of 2,7-DHN incorporated into CP44 is in a pseudo-axial mode with the long axis of its naphthalene ring penetrating the cavity obliquely.[36] Thus, a slight difference in the binding mode between the steroid cyclophane and CP44 partly comes from changes in the bond characters of four nitrogen atoms in the macrocycle, that is, whether they are amide or amino nitrogens. The larger binding constant for a complex composed of CP44 and 2,7-DHN ($K=2{\cdot}8\times10^3$ dm^3 mol^{-1} in D_2O at pD 1·2 and 301 K)[36] to that for the **3**–2,7-DHN complex supports such an interpretation. However, a more dominant effect is presumably provided by the rigid hydrophobic branches. The four hydrophobic branches of the steroid cyclophane seem to force the guest to align its longer molecular axis parallel to the molecular axis of the host.

On the other hand, the guest-binding mode of the octopus cyclophane is very different from that of the steroid cyclophane; the extents of upfield shifts of the guest signals

Table 1. Binding constants (K), free energies of complexation ($\Delta G°$) and CIS values for 2,7-DHN with cyclophane hosts in D_2O[a]

				CIS (ppm)		
Host	Temperature (K)	K(dm^3 mol^{-1})	$\Delta G°$ (kJ mol^{-1})	1-H	3-H	4-H
1	303	4200	−21·0	−1·52	−0·63	−1·48
1	343	1900	−21·5	−0·73	−0·43	−0·78
2	343	1630	−21·1	−0·17	−0·22	−0·38
3	303	490	−15·6	−1·60	−0·60	−1·56

[a]Concentrations in mol dm^{-3}: 2,7-DHN, $1{\cdot}0\times10^{-3}$; cyclophanes, $2{\cdot}5\times10^{-4}$–$3{\cdot}0\times10^{-3}$. Medium pH: 5·0, 7·6 and 6·5 for **1**, **2** and **3**, respectively. Values of temperature, K, $\Delta G°$ and CIS are accurate to within ±0·1 K, ±5%, ±0·2 kJ mol^{-1} and ±0·02 ppm, respectively.



Formula 3.

decrease in the order 4-H > 3-H > 1-H for **2** and the CIS values are relatively small. The results indicate that the 2,7-DHN molecule is present floating in the hydrophobic three-dimensional space created by the macrocyclic skeleton and the flexible hydrocarbon chains, as shown in Figure 2(b).

Next, we evaluated the recognition behavior of the modified cyclophanes towards 8-anilinonaphthalene-1-sulfonate (ANS) by means of fluorescence spectroscopy. The steroid cyclophane and the octopus cyclophane are known to markedly enhance the emission intensity originating from ANS and to induce a blue shift of its fluorescence maximum upon complexation.[24,29] We focused here on the temperature dependence of the molecular recognition behavior in aqueous media. Binding constants (K) for 1:1 host–guest complexes of the cyclophanes with ANS and the corresponding free energy changes ($\Delta G°$) were evaluated for the temperature range 295–335 K in a manner similar to that reported previously.[29] The results are summarized in Table 2 along with the emission maxima (λ_{max}) for ANS bound to the hosts; the λ_{max} value in water without any host is 515 nm.

The K and λ_{max} values for ANS bound to CP44 were reported to be $6{\cdot}3\times10^3$ dm^3 mol^{-1} and 500 nm, respectively, in KCl–HCl buffer at pH 1·95 and 298 K.[39] With regard to recognition of the ANS molecule, which is more bulky than 2,7-DHN, the introduction of hydrophobic branches, such as rigid cholate moieties or flexible hydrocarbon chains, into the macrocyclic skeleton resulted in a marked enhancement of the binding ability towards the hydrophobic guest.

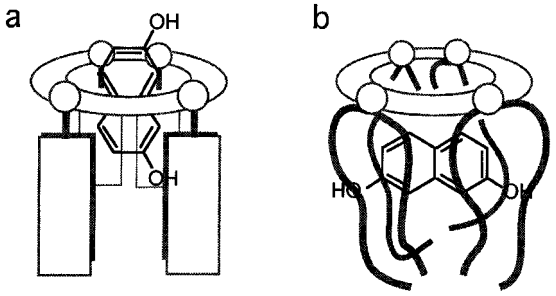


Figure 2. Schematic representation of geometries of the host–guest complexes of 2,7-DHN with (a) **1** and (b) **2**

When R ln K was plotted against $1/T$ on the basis of the typical van't Hoff equation:

$$R \ln K = -\Delta H°(1/T) + \Delta S° \quad (1)$$

a good linear relationship with a correlation coefficient $r = 0.999$ was obtained for the **1**–ANS complex system and the thermodynamic parameters were evaluated as $\Delta H° = -18.3$ kJ mol^{-1} and $\Delta S° = 36{\cdot}0$ J mol^{-1} K^{-1}. On the other hand, the corresponding plot for the **2**–ANS complex system did not show a linear relationship ($r = 0{\cdot}970$). This indicates that a change in heat capacity upon complexation at constant pressure [$\Delta C_p° = (\mathrm{d}\Delta H°/\mathrm{d}T)_p$] cannot be neglected for the present system. Hence the thermodynamic parameters need to be analyzed on the basis of Eqn (2) allowing for the effect of a temperature-invariant heat capacity change in place of Eqn (1):

$$R \ln K = -\Delta H_0(1/T) + \Delta C_p° \ln T + (\Delta S_0 - \Delta C_p°) \quad (2)$$

where ΔH_0 and ΔS_0 are constants of integration: $\Delta H° = \Delta H_0 + T\Delta C_p°$ and $\Delta S° = \Delta S_0 + \Delta C_p°$ ln T.[40] By using a numerical curve-fitting procedure with three adjustable parameters, the thermodynamic parameters for the **2**–ANS complex system were evaluated as $\Delta H° = -10{\cdot}6$ kJ mol^{-1} and $\Delta S° = 88{\cdot}0$ J mol^{-1} K^{-1} at 298 K and $\Delta C_p° = -1160$ J mol^{-1} K^{-1}.

In general, the $\Delta C_p°$ values for the complexation of rigid macrocyclic compounds such as cyclophanes and cyclodextrins with hydrophobic guests in aqueous media have been reported to be in the range -50 to -800 J mol^{-1} K^{-1}.[40–42] Accordingly, the $\Delta C_p°$ value for the **2**–ANS complex system is larger than those for these host–guest systems and comparable to those for interactions of proteins with small ligands such as binding of a coenzyme or a substrate to an apoenzyme; the $\Delta C_p°$ values are in a range -350 to -1700 J mol^{-1} K^{-1}.[43,44] Although the large and negative $\Delta C_p°$ value observed for the guest binding of the octopus cyclophane may be partly attributable to the hydrophobic effect,[42,44] the induced-fit character of the octopus cyclophane would make an additional contribution to the heat capacity. On the other hand, the $\Delta C_p°$ value is ignored for the binding of ANS by the steroid cyclophane, suggesting that some other effects are involved to compensate for the decrease in the $\Delta C_p°$ value by the hydrophobic interaction. We have recently clarified that **1** can recognize guest molecules through hydrogen-bonding interactions in addition to hydrophobic and electrostatic effects.[27] Hence the formation of hydrogen bonds upon complexation may be

one of the effects that act to increase the ΔC_p° value.

The positive ΔS° values for the present host–guest complexation must come from effective desolvation of the guest molecule incorporated into the host cavities and partly from conformational changes of the hosts owing to the induced-fit binding of the guest molecule. Since, as described below, the desolvation effects seem to be comparable to each other between the steroid cyclophane and the octopus cyclophane as evaluated from the λ_{max} values, the ΔS° difference primarily reflects a difference in conformational change between both hosts when the induced-fit binding takes place.

The λ_{max} values measured at various temperatures for ANS bound to the host, **1** or **2**, as listed in Table 2 are much smaller than those for the identical guest bound to CP44 (λ_{max} = 500 nm). The results indicate that the guest-binding sites of both cyclophanes are well desolvated and significantly hydrophobic. It is noteworthy that the λ_{max} value for ANS bound to the steroid cyclophane was independent of temperature whereas the value for the identical guest bound to the octopus cyclophane was gradually shifted to longer wavelength when the temperature was raised. Hence the guest binding site of the steroid cyclophane seems to be relatively rigid whereas that of the octopus cyclophane is presumably rather soft.

In order to obtain further insights into microenvironmental properties around the guest binding sites provided by these cyclophane derivatives, the rotational correlation time (θ) of the guest incorporated into the host was evaluated from the observed values of the steady-state fluorescence polarization (P) and fluorescence lifetime (τ) on the basis of Perrins equation:[45]

Table 2. Temperature dependence of binding constant (K), free energy of complexation (ΔG°) and emission maximum (λ_{max}) for ANS with cyclophane hosts in aqueous acetate buffer (1.0×10^{-2} mol dm^{-3}) at pH 5·0[a]

Host	Temperature (K)	K (dm^3 mol^{-1})	ΔG° (kJ mol^{-1})	λ_{max} (nm)
1	295	$1{\cdot}30\times10^5$	−28·9	471
	303	$1{\cdot}10\times10^5$	−29·2	471
	311	$8{\cdot}77\times10^4$	−29·4	471
	319	$7{\cdot}52\times10^4$	−29·8	471
	327	$6{\cdot}29\times10^4$	−30·0	471
	335	$5{\cdot}40\times10^4$	−30·4	471
2	295	$3{\cdot}06\times10^6$	−36·6	466
	303	$2{\cdot}53\times10^6$	−37·1	467
	312	$2{\cdot}02\times10^6$	−37·7	469
	318	$1{\cdot}75\times10^6$	−38·0	471
	326	$1{\cdot}14\times10^6$	−37·8	473
	335	$7{\cdot}12\times10^5$	−37·5	476

[a]Concentrations in mol dm^{-3}: ANS, $1{\cdot}0\times10^{-6}$ and $2{\cdot}0\times10^{-7}$ for complexation with **1** and **2**, respectively; **1**, $4{\cdot}0\times10^{-6}$–$3{\cdot}0\times10^{-5}$; **2**, $4{\cdot}0\times10^{-7}$–$3{\cdot}0\times10^{-6}$. Excitation wavelength, 375 nm. Values of temperature, K, ΔG° and λ_{max} are accurate to within ±0·1 K, ±3%, ±0·1 kJ mol^{-1} and ±0·5 nm, respectively.

Table 3. Temperature dependence of steady-state fluorescence polarization values (P) and fluorescence lifetime (τ) for ANS bound to cyclophane hosts in aqueous acetate buffer (1.0×10^{-2} mol dm^{-3}) at pH 5·0[a]

Host **1**			Host **2**		
Temperature (K)	P	τ (ns)	Temperature (K)	P	τ (n/s)
292	0·075	14·0	292	0·318	13·4
303	0·069	13·6	302	0·298	12·1
312	0·056	12·5	312	0·282	11·4
320	0·053	11·9	321	0·261	10·8
330	0·045	11·6	330	0·235	10·0
336	0·037	10·9	335	0·221	9·6

[a]Concentrations in mol dm^{-3}: ANS, $1{\cdot}0\times10^{-6}$ and $2{\cdot}0\times10^{-7}$ for complexation with **1** and **2**, respectively; **1**, $1{\cdot}0\times10^{-5}$; **2**, $2{\cdot}0\times10^{-6}$. Excitation wavelength, 375 nm. Values of temperature, P and τ are accurate to within ±0·1 K, ±0·002 and ±0·3 ns, respectively.

$$1/P - 1/3 = (1/P_0 - 1/3)(1 + \tau/\theta) \quad (3)$$

where P_0 is the maximum value of P for a guest without any rotational motion; $P_0 = 0{\cdot}427$[30] for ANS. The P and τ values for ANS bound to **1** and **2** measured at various temperatures are listed in Table 3, and the θ values are temperature dependent, as shown in Figure 3. Although the host–guest complexes are not completely formed under the conditions specified in Table 3, the fluorescence intensity due to the free guest is extremely weak (less than 1%) relative to that due to the bound guest. Hence the contribution of the free guest to the P value can be neglected for both cyclophane systems in the temperature range employed.

Since the τ value for ANS in water is 0·55 ns,[46] the

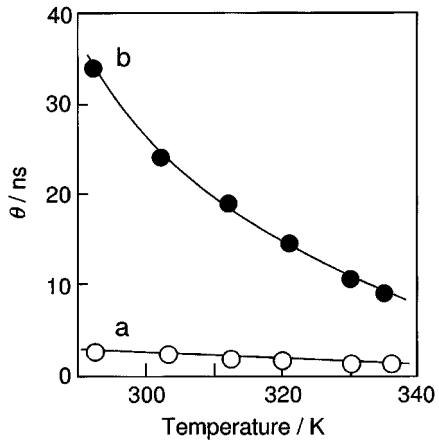
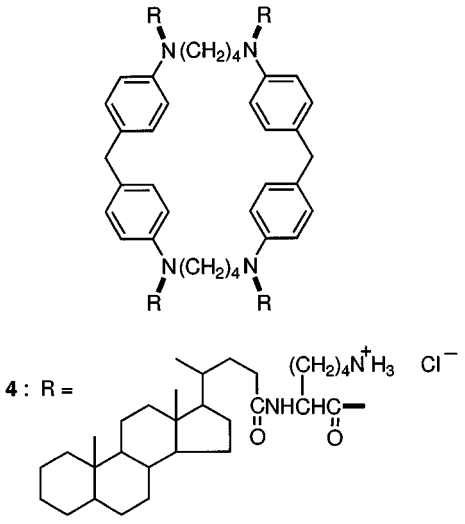


Figure 3. Temperature dependence of rotational correlation times for ANS bound to (a) **1** and (b) **2** in aqueous acetate buffer (1.0×10^{-2} mol dm^{-3}) at pH 5·0. Values of K and θ are accurate within ±0·1 K and ±5%, respectively

fluorescence lifetime of the guest was extremely prolonged upon complexation with these host molecules, reflecting well the desolvated and hydrophobic properties of the binding sites of both hosts. While the τ values for ANS bound to **1** and **2** are comparable to each other, there are large differences in the *P* value between the hosts. Thus, the θ value for ANS bound to the octopus cyclophane is much larger than that for the guest bound to the steroid cyclophane. In addition, a marked temperature dependence of the θ value for ANS was observed upon complex formation with the octopus cyclophane; the molecular motion of the guest is extremely restricted at low temperatures. On the other hand, the guest molecule is more loosely bound to the steroid cyclophane, as reflected by the θ value. When **1** was replaced with another steroid cyclophane lacking hydroxyl groups on the steroid moiety (**4**),[27] the following values were obtained for complexation with ANS: $K = 4{\cdot}2 \times 10^4$ dm^3 mol^{-1}, $\lambda_{max} = 464$ nm $P = 0{\cdot}242$, $\tau = 15{\cdot}9$ ns and $\theta = 17{\cdot}9$ ns at 303 K. As for steroid cyclophane **1**, the hydroxyl groups on the steroid moieties play a specific role in binding the guest molecule as reflected by the binding constant and the rotational correlation time.

In conclusion, we have demonstrated the unique guest-binding behavior of two artificial hosts, steroid cyclophane **1** and octopus cyclophane **2**. Each host provides a three-dimensionally extended hydrophobic cavity created by a macrocyclic skeleton and four hydrophobic branches in aqueous media. While both hosts bind aromatic guests with large binding constants, their guest-binding modes are different from each other. The steroid cyclophane provides a rigid hydrophobic space maintaining characteristic molecular recognition capability by the macrocyclic skeleton. On the other hand, the octopus cyclophane provides a highly viscous microenvironment owing to its potent induced-fit character. These host molecules are expected to display their respective individualities in various supramolecular processes as artificial enzymes or receptors.



Formula 4.

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