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Inclusion behavior of azacyclophanes holding various hydrophobic cavities

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Abstract - Azacyclophane derivatives with some hydrophobic modifications were prepared, and their inclusion behavior was characterized as artificial hosts. A cubic cyclophane which provides a relatively rigid and large hydrophobic cavity surrounded by six faces, each being constructed with the [3.3.3.3]paracyclophane ring, affords stable host-guest (1:1) complexes with organic solvent molecules such as chloroform and benzene. In aqueous media, host molecules bearing flexible hydrocarbon branches provide cavities that are deep and hydrophobic enough to incorporate hydrophobic guests of various bulkiness through an induced-fit mechanism. The pyrene-sensitized photochemical reaction of 2-azidobiphenyl was much enhanced in a hydrophobic cage provided by an octopus cyclophane having eight hydrocarbon chains, due to effective formation of a ternary complex.

INTRODUCTION

Cyclophanes with a sizable internal cavity behave as artificial host molecules capable of exhibiting molecular recognition. In view of current interest in host-guest chemistry, various cyclophane derivatives have been prepared (ref. 1). Although rigid macrocyclic skeletons of such molecules are generally used to aim at regiospecific host-guest interactions, the hydrophobic cavity of cyclophanes constituted with a simple macrocyclic ring is relatively small and shallow. On the other hand, naturally occurring hosts such as enzymes discriminate various guest molecules by their three-dimensionally designed and significantly desolvated hydrophobic cavities and exhibit excellent guest-binding behavior relative to the artificial host molecules. To improve molecular recognition ability of cyclophanes, we adopted the following hydrophobic modifications for the tetraaza[3.3.3.3]paracyclophane ring, as schematically shown in Fig. 1: type 1, azacyclophanes without hydrophobic modifications; type 2, azacyclophanes bearing four hydrophobic branches with either flexible or rigid character; type 3, azacyclophanes having eight hydrocarbon chains (octopus cyclophanes); type 4, a host molecule composed of two rigid macrocyclic skeletons which are connected to each other with four flexible hydrocarbon chains; type 5, a host molecule having a relatively rigid and large three-dimensional hydrophobic cavity. This article describes preparation of various azacyclophane derivatives and their characteristic guest-binding behavior.

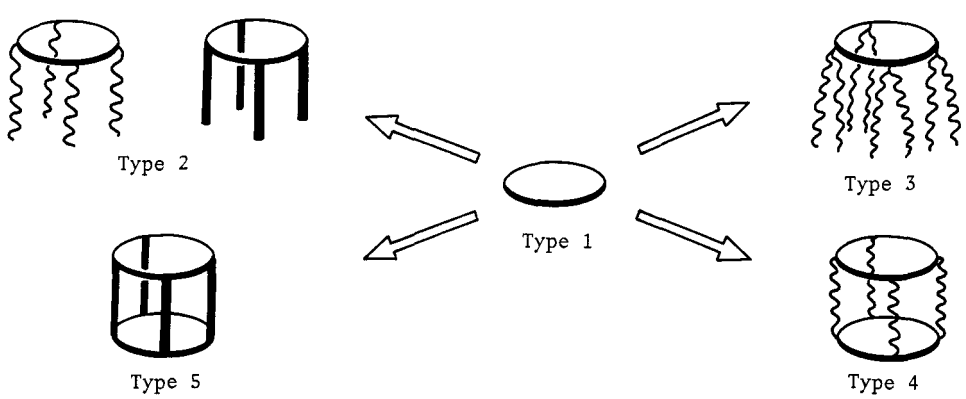


Fig. 1. Schematic representations for cyclophanes having various hydrophobic cavities designed three-dimensionally by using flexible (∿∿∿) or rigid (▬) building blocks: ⬭ denotes a macrocyclic ring.

PREPARATION OF AZACYCLOPHANE HOSTS

Type 1

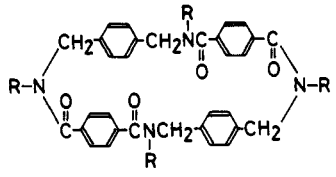
N,N',N'',N'''-Tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane-1,12,19,30-tetraone (1) was prepared by the condensation of N,N'-dimethyl-p-xylylenediamine with terephthaloyl dichloride under high dilution conditions, and the subsequent reduction of 1 with lithium aluminum hydride gave N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (8) (ref. 2). 2,11,20,29-Tetraaza[3.3.3.3]paracyclophane (7) was obtained by the coupling reaction of 1,4-bis(chloromethyl)benzene with p-toluenesulfonamide in the presence of sodium hydride, followed by removal of the tosyl groups of N,N',N'',N'''-tetratosyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane with sodium/liquid ammonia, in a manner similar to that reported by Inazu et al. (ref. 3).

Type 2

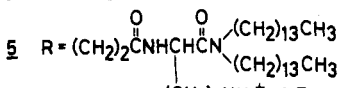
Azacyclophanes having short or long hydrocarbon branches, N,N',N'',N'''-tetrakis(2-carboxyethyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane-1,12,19,30-tetraone (2), N,N',N'',N'''-tetrakis(10-carboxydecyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane-1,12,19,30-tetraone (3), and N,N',N'',N'''-tetrakis(10-trimethylammoniodecyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane-1,12,19,30-tetraone tetraiodide (4), were prepared from N,N'-disubstituted p-xylylenediamine derivatives with terephthaloyl dichloride as described previously (ref. 2, 4, & 5). N,N',N'',N'''-Tetrakis(4-carboxybenzoyl)-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (9), bearing four rigid branches, were obtained by the condensation of 7 with methyl 4-chloroformylbenzoate and the subsequent alkaline hydrolysis (ref. 6).

Type 3

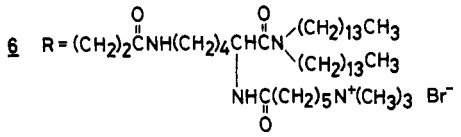
As regards the synthesis of N,N',N'',N'''-tetrakis[2-[N-[1-(N,N-ditetradecylcarbamoyl)-5-(ammoniopent-1-yl)]carbamoyl]ethyl]-2,11,20,29-tetraaza[3.3.3.3]paracyclophane-1,12,19,30-tetraone tetrachloride (5), an octopus cyclophane having eight hydrocarbon chains and four amino groups, the tetraacid chloride form of 2 underwent reaction with N,N-ditetradecyl-N^{ε}-benzyloxycarbonyl-L-lysinamide and the benzyloxycarbonyl groups were subsequently removed (ref. 7). Meanwhile, another octopus cyclophane possessing four quaternary ammonium moieties on the polar segments, N,N',N'',N'''-tetrakis[2-[N-[1-(N,N-ditetradecylcarbamoyl)-[5-(trimethylammonio)pentanecarboxamide]pent-5-yl]carbamoyl]ethyl]-2,11,20,29-tetraaza[3.3.3.3]paracyclophane-1,12,19,30-tetraone tetrabromide (6), was obtained by the condensation of the acid chloride form of 2 with N,N-ditetradecyl-N^{α}-[6-(trimethylammonio)hexanoyl)-L-lysinamide bromide.



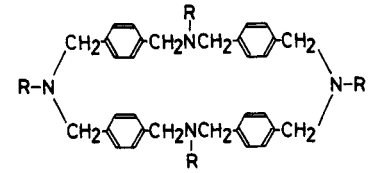
1 R = CH_3
2 R = $(CH_2)_2CO_2H$
3 R = $(CH_2)_{10}CO_2H$
4 R = $(CH_2)_{10}N^+(CH_3)_3$ I^-



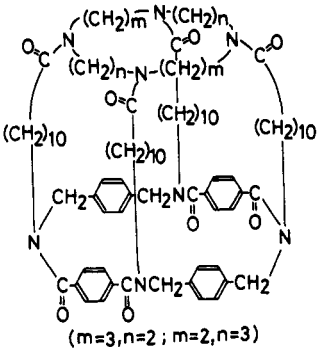
5 R = $(CH_2)_2CNHCHCN(CH_2)_{13}CH_3$, $(CH_2)_{13}CH_3$, $(CH_2)_4NH_3^+$ Cl^-



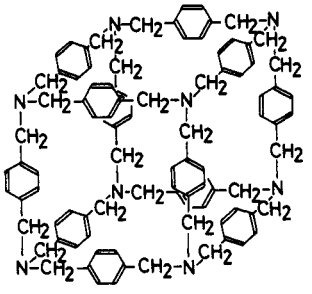
6 R = $(CH_2)_2CNH(CH_2)_4CHCN(CH_2)_{13}CH_3$, $(CH_2)_{13}CH_3$, $NHC(CH_2)_5N^+(CH_3)_3$ Br^-



7 R = H
8 R = CH_3
9 R = $C(=O)C_6H_4CO_2H$



(m=3,n=2 ; m=2,n=3)
10



11

Type 4

The host molecule (10) was synthesized by the condensation of the corresponding tetraacid chloride of 3 with 1,4,8,11-tetraazacyclotetradecane under high dilution conditions (ref. 8).

Type 5

The cubic cyclophane (11) which provides a hydrophobic cavity surrounded by six faces, each being constructed with the 2,11,20,29-tetraaza[3.3.3.3]paracyclophane ring, was prepared by the reaction of the tetraacid chloride of 9 with 7 under high dilution conditions and the subsequent reduction with borane-dimethylsulfide (ref. 9).

INCLUSION BEHAVIOR IN SOLID STATE

It has been reported that host-guest (1:1) molecular complexes were formed with 8 and various organic molecules, such as benzene, dioxane, chloroform, and dichloromethane, in the solid state (ref. 9, 10, & 11). Since each face of the cubic cyclophane (11) is constructed with a macrocyclic ring similar to that of 8, formation of host-guest complexes of 11 with various organic molecules is also expected. When 11 was recrystallized from benzene, we obtained the 11-benzene (1:1) adduct, which was identified by elemental analysis, ^{1}H NMR, and IR spectroscopy. This host molecule also incorporated chloroform into it at the 1:1 molar ratio. We examined the stability of the resulting complex by means of IR spectroscopy. Tabushi et al. reported that the host-guest inclusion complex of 8 with chloroform in the crystalline state was destroyed with the concomitant total loss of the guest upon heating at 80 °C/0.5 mmHg for 4 h (ref. 11). On the other hand, the intensity of C-Cl stretching at 760 cm^{-1} for the complex of 11 with chloroform unchanged even after 4 h of heating at 100 °C/0.1 mmHg. The IR intensity gradually decreased at 100 °C/0.05 mmHg, and the band disappeared completely after 18 h of heating. Thus, it seems that the cubic cyclophane strongly incorporates organic guest molecules into its hydrophobic cavity at the 1:1 molar ratio in the solid state. In contrast, formation of the inclusion complex of 11 with two solvent molecules in chloroform solution was suggested in view of molecular weight measurements by osmometry.

INCLUSION BEHAVIOR IN AQUEOUS MEDIA

The guest-binding behavior of the azacyclophanes was examined by fluorescence and electronic absorption spectroscopy in the following aqueous buffers (0.01 mol dm^{-3}, μ 0.10 with KCl) at 30.0 °C: acetate, 2-(N-morpholino)ethanesulfonate (MES), 2-[4-(2-hydroxyethyl)piperazin-1-yl]-ethanesulfonate (HEPES), and 3-(cyclohexylamino)propanesulfonate (CAPS) for pH 3.0, 6.0, 8.0, and 10.0, respectively. The following hydrophobic probes were chosen as guest molecules: 8-anilinonaphthalene-1-sulfonate (12), 6-p-toluidinylnaphthalene-2-sulfonate (13), pyrene-1-butanoate (14), 1-phenylazo-2-naphthol-6,8-disulfonate (15), and indole-3-acetate (16) as anionic ones; N-phenyl-1-naphthylamine (17), 1-(2-pyridylazo)-2-naphthol (18), N-benzyl-1,4-dihydronicotinamide (19), indole (20), and pyrene (21) as nonionic ones; 1-dimethylamino-naphthalene-5-sulfonamidoethyltrimethylammonium (22) and 2-(p-dimethylaminostyryl)-1-ethyl-quinolinium (23) as cationic ones.

In general, electronic spectra of the guest molecules were measured by changing concentrations of the host molecules. Binding constants for the formation of inclusion complexes of the hosts with various guest molecules at the 1:1 molar ratio (K_1) were calculated on the basis of the Benesi-Hildebrand-type relationship as described previously (ref. 12). The

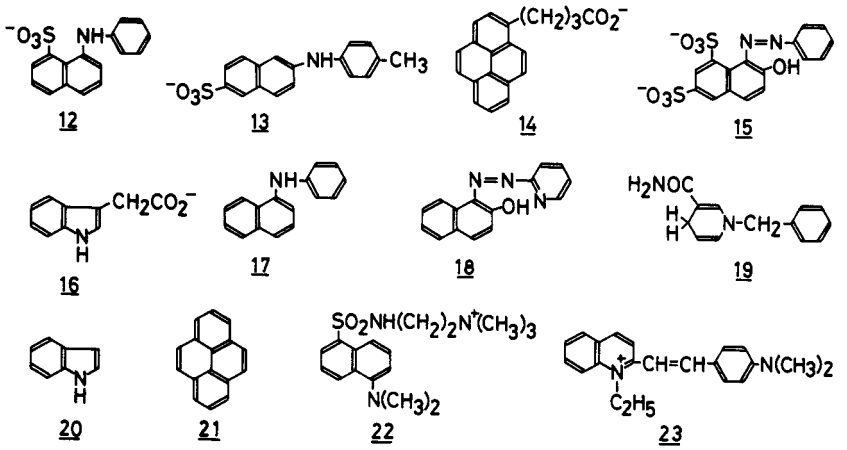


TABLE 1. Binding constants (K_1/dm^3 mol^{-1}) for inclusion of various guest molecules by cyclophanes in aqueous media at 30.0 °C[a]

Guest	Method[b]	Host[c]							
		2	3	4	5	6	9	10	11
12	F	—— [d]	—— [d]	1.1×10^4	2.8×10^5	2.5×10^5		1.7×10^4	1.0×10^4
13	F			7.5×10^3	3.0×10^5	4.7×10^5		9.1×10^3	3.0×10^4
14	F					9.1×10^5			
15	E			5.2×10^2	1.4×10^5				
16	F	2.0×10^2	1.0×10^2						
17	F	—— [d]	1.6×10^3	4.6×10^3	1.3×10^6	2.6×10^5	6.2×10^2	5.1×10^4	
18	E			3.2×10^2	3.7×10^5				
19	F	—— [d]	2.0×10^3						
20	F	1.5×10^3	1.5×10^3						
21	F					1.2×10^6 ($K_2=2.4\times10^6$)			
22	F			—— [d]	—— [d]	—— [d]			
23	E			—— [d]	—— [d]	—— [d]			—— [d]

[a]Concentrations in mol dm^{-3}: 12, 13, 14, 17, 21, and 22, 1.0×10^{-6}; 15, 16, 18, 19, 20, and 23, 1.0×10^{-5}; 2, 3, and 9, 5.0×10^{-5}—5.0×10^{-4}; 4, 5.0×10^{-5}—3.0×10^{-4}; 5 and 6, 5.0×10^{-6}—3.0×10^{-5}; 10 and 11, 1.0×10^{-5}—1.0×10^{-4}.
[b]F, fluorescence spectroscopy; E, electronic absorption spectroscopy.
[c]pH values for measurements: 2, 3, and 9, 10.0; 4 and 5, 6.0; 6 and 10, 8.0; 11, 3.0.
[d]Complex formation was not detected.

binding constants for the inclusion of these guest molecules by the hosts are listed in Table 1. The K_1 values for the type 1 hosts with various guest molecules are too small to be evaluated accurately by electronic spectroscopy. Meanwhile, hydrophobic guest molecules are effectively incorporated into the type 2 hosts primarily through the hydrophobic interaction. In addition, the guest recognition through electrostatic and charge-transfer interactions becomes effective by introduction of additional functional sites into the host. The flexible and long hydrocarbon chains introduced into a rigid macrocyclic skeleton effectively constitute a relatively large hydrophobic binding site. The K_1 values for the type 3 hosts with the anionic and nonionic guests are 1—3 order of magnitude greater than the corresponding values for the type 2 hosts due to the increased hydrophobic effect exercised by the former hosts. Moreover, the hydrophobic cage provided by the octopus cyclophane is highly apolar and acts to repress the molecular motion of guest molecules. The hosts of types 4 and 5 also exhibit relatively large guest-binding affinity. Difference in molecular flexibility between these host molecules is reflected on their microenvironmental polarities around the incorporated guest molecules, and 10 and 11 provide for 12 microenvironments nearly equivalent to those provided by tetrahydrofuran [$E_T(30)$, 37.4 kcal mol^{-1}] and methanol [$E_T(30)$, 55.5 kcal mol^{-1}], respectively.

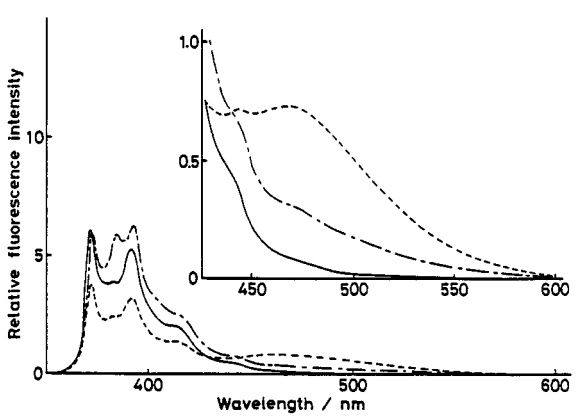


Fig. 1. Fluorescence spectra of 21 (1.0×10^{-6} mol dm^{-3}) upon addition of 6 in an aqueous HEPES buffer at pH 8.0 and 30.0 °C; excitation wavelength, 337 nm. Concentrations of 6 in mol dm^{-3}: ——, 0; -----, 1.0×10^{-6}; —·—·—, 3.1×10^{-5}.

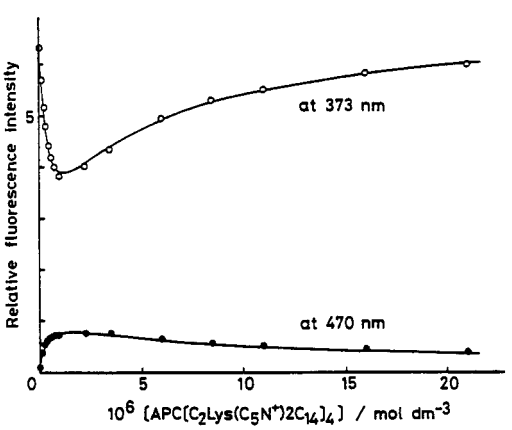


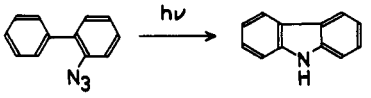
Fig. 2. Correlations of intensities of the monomer (o) and excimer (o) species of 21 (1.0×10^{-6} mol dm^{-3}) with concentration of 6 in an aqueous HEPES buffer at pH 8.0 and 30.0 °C. Solid lines refer to the calculated data.

The inclusion behavior of 6 toward 21 was somewhat different from that toward other guest molecules as clarified by fluorescence spectroscopy. A dilute aqueous solution of 21 (1.0×10^{-6} mol dm^{-3}) showed emission originated from the monomer species. However, a broad emission band, which is attributed to the pyrene excimer, appeared in a longer wavelength region (λ_{max}, 470 nm) with a concomitant decrease of the monomer emission upon addition of 6 in the concentration range of 1.25×10^{-7}—1.0×10^{-6} mol dm^{-3} (Fig. 1). The excimer and monomer emissions reached a maximum and a minimum intensity, respectively, at the cyclophane concentration of 1.0×10^{-6} mol dm^{-3}, and then the former intensity decreased gradually and the latter intensity increased in a parallel manner as the host was added further (Figs. 1 & 2). The fluorescence behavior indicates the formation of two kinds of the inclusion complexes, 1:1 and 1:2 (host : guest) species. Thus, the formation constants for the 1:1 and 1:2 complexes (K_1 and K_2, respectively) were calculated from the fluorescence intensities measured at 373 and 470 nm, respectively, (Fig. 2); $K_1 = 1.2 \times 10^6$ and $K_2 = 2.4 \times 10^6$ dm^3 mol^{-1}. Thus, the octopus cyclophane favors the formation of both 1:1 and 1:2 complexes to a remarkable and comparable extent due to the induced-fit binding mode. This binding behavior is in contrast to that of γ-cyclodextrin having a rigid hydrophobic cavity; the formation constant for the 1:2 host-guest complex with 21 is markedly greater than that for the 1:1 complex (ref. 13).

CATALYTIC FUNCTIONS

As mentioned above, the hydrophobic cage provided by the octopus cyclophane is highly apolar and acts to repress the molecular motion of guest molecules. In order to characterize the hydrophobic cavity of this cyclophane as a reaction site, we studied on the photochemical reaction of 2-azidobiphenyl (24) in the presence and absence of 6 in aqueous media at 20 °C under anaerobic conditions. At a lower concentration of 24 employed in this study (5.0×10^{-5} mol dm^{-3}), 25 was the only product as confirmed by electronic absorption spectroscopy and HPLC analysis (Scheme 1). The observed rate constants for the formation of 25 in the presence and absence of 6 and 21 as a host and a sensitizer, respectively, (ref. 14) are listed in Table 2. Although the reaction rate was somewhat enhanced in the presence of 21 (5.0×10^{-5} mol dm^3) in a homogeneous aqueous solution, an addition of the octopus cyclophane to this system resulted in significant rate enhancement. Since the reactivity was not affected by the presence of the octopus cyclophane alone, such rate enhancement must come from efficient formation of the ternary complex composed of 6, 21, and 24 as schematically shown in Fig. 3.

Scheme 1



24 25

TABLE 2. Reactivity of 24 (5.0×10^{-5} mol dm^{-3}) in ethanol—water (4:96 v/v) at 20 °C under anaerobic photolysis conditions

6/10^{-5} mol dm^{-3}	21/10^{-5} mol dm^{-3}	$k_{obs}/10^{-4}$ s^{-1}	k_{rel}
10	5.0	23	12
5.0	2.5	12	6.3
5.0	0	2.0	1.1
0	5.0	4.2[a]	1.8
0	0	1.9 (2.3[a])	1

[a]In ethanol—water (1:1 v/v).

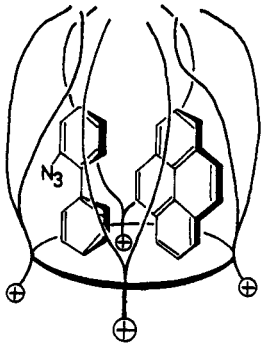
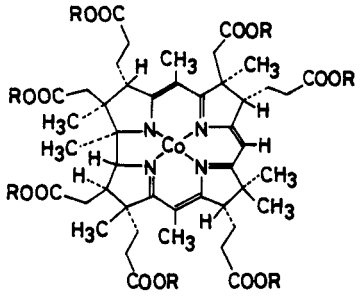


Fig. 3. Schematic representation of the reactive ternary complex composed of 6, 21, and 24.



R=C_3H_7

26

The results imply that the octopus cyclophane can be utilized as a novel apoenzyme model. As one of the approaches along this line, we have recently constituted an artificial holoenzyme composed of 6 and a hydrophobic vitamin B_{12} derivative (26) and demonstrated that such a host-guest complex acted as an effective model for functional simulation of the vitamin B_{12}-dependent methylmalonyl-CoA mutase (ref. 15).

CONCLUSION

We clarified here some novel aspects in designing hydrophobic macrocycles which may undergo effective host-guest interactions in aqueous media. The guest-binding sites provided by the hosts of types 3 and 4 are highly apolar and act to repress the molecular motion of the incorporated guest molecules. On the other hand, the type 5 host is cited as an excellent host, which can be treated with various guests in the solid state, and expected to exercise rigorous molecular discrimination superior to the other hosts.

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