Tetraoxotetraazaparacyclophanes with Various Alkyl Chains as Hosts for Hydrophobic Compounds

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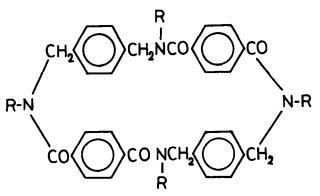
Synopsis. Tetraoxotetraazaparacyclophanes with short or long alkyl chains and tertiary amino groups were synthesized. It was shown that *NN'N''N'''*-tetrakis-(3-dimethylaminopropyl)-3,10,21,28-tetraoxo-2,11,20,29-tetraaza[3.3.3.3]paracyclophane and *NN'N''N'''*-tetrakis-(5-dimethylaminopentyl)-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza-[3.3.3.3]paracyclophane as well as *NN'N''N'''*-tetrakis-(10-dimethylaminodecyl)-3,10,21,28-tetraoxo-2,11,20,29-tetra-aza-[3.3.3.3]paracyclophane could undergo a complex formation with picrate and 8-anilino-1-naphthalenesulfonic acid, while the dissociation constants for the former cyclophanes were larger than those for the latter cyclophane. The hydrolysis of *p*-nitrophenyl hexanoate was also studied in the presence of the cyclophanes and azide ion (N_3^-), but the reaction was not significantly activated.

Chemical reactions in vivo are catalyzed by enzymes, where host-guest complexes are formed between substrates and enzymes before reactions take place. Another typical example of host-guest complexes can be seen in antigen-antibody reactions. Murakami et al. designed several tetraoxotetraazaparacyclophanes possessing four or eight long alkyl chains (octopus azaparacyclophanes) and characterized the complex formation with hydrophobic compounds.[1-3] Other types of water-soluble cyclophanes were synthesized by Tabushi et al.[4,5] and Odashima et al.,[6] which could undergo complex formations with some hydrophobic anionic compounds.

In the present work, we have studied the former type of cyclophanes, which have shorter alkyl chains than those characterized by Murakami et al.[1-3] and have tertiary amino groups. The substrate-binding ability of such tetraoxotetraazaparacyclophanes with shorter alkyl chains has not been studied so far.



R = $(CH_2)_n$-N(CH_3)(CH_3)

1: n=3
2: n=5
3: n=10

Experimental

Tetraoxotetraazaparacyclophanes (**1**, **2**, **3**) were synthesized in a similar manner as reported.[1,2] Potassium picrate (Kanto Chemical Co.), 8-anilino-1-naphthalenesulfonic acid magnesium salt (ANS) (Nakarai Chemicals) and *p*-nitrophenyl hexanoate (*p*-NPH) (Tokyo Kasei Kogyo Co.) were used as supplied. Other reagents used were of the purest grade available.

Electronic absorption and fluorescence spectra were taken on a Beckman Model 34 spectrophotometer and a JASCO FP-4 fluorescence spectrophotometer, respectively, at pH 6.3 (0.1 mol dm^{-3} Na_2HPO_4–0.1 mol dm^{-3} NaH_2PO_4 buffer) and 25 °C. The hydrolysis of *p*-NPH was investigated under the conditions: pH 8.1 (0.05 mol dm^{-3} NaH_2PO_4–0.025 mol dm^{-3} $Na_2B_4O_7$ buffer), μ=0.1 (KCl) and 32 °C. The reaction rate was determined by measuring the absorbance at 400 nm, originating from the liberated *p*-nitrophenol, with a Beckman Model 34 spectrophotometer.

Results and Discussion

The absorption spectrum of potassium picrate changed upon the addition of **1**, **2**, or **3**. Typical spectral changes caused by **3** are shown in Fig. 1. By assuming the formation of a 1:1 complex between picrate and the cyclophane, the dissociation constants (K_d) were evaluated by the Benesi-Hildebrand plot[1] and are summarized in Table 1. In Fig. 2 is shown a typical plot for **1**. It should be noted that **1** and **2** form relatively stable complexes with picrate but their dissociation constants are larger than that with **3**.

It is generally known that the fluorescence intensity of ANS is significantly increased when it is situated in hydrophobic environments.[7] Thus, the dissociation constants for the complexes formed with ANS and the cyclophanes were obtained from the fluorescence measurements. Figure 3 shows the typical Benesi-

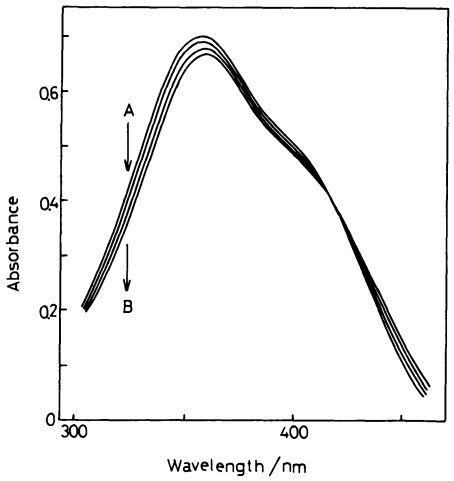


Fig. 1. Absorption spectra of potassium picrate at various concentrations of **3**: pH 6.3(0.1 mol dm^{-3} Na_2HPO_4–0.1 mol dm^{-3} NaH_2PO_4 buffer); 25 °C. The concentrations(mol dm^{-3}) of **3** are 0, 5×10^{-6}, 5×10^{-5} and 1×10^{-4}; read from A to B. The concentration of potassium picrate is 5×10^{-5} mol dm^{-3}.

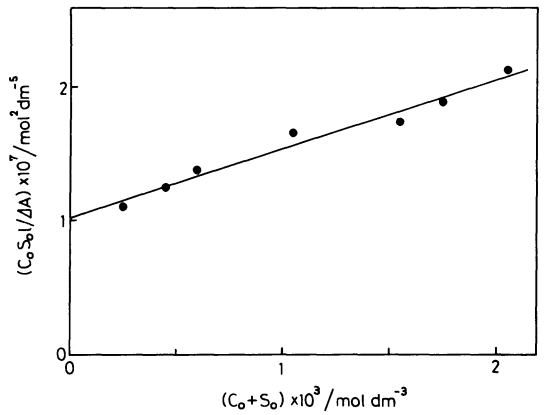


Fig. 2. Benesi–Hildebrand plot for the complex formation between potassium picrate and **1**: pH 6.3(0.1 mol dm^{-3} Na_2HPO_4–0.1 mol dm^{-3} NaH_2PO_4 buffer); 25 °C.
C_0: Concentration of **1**.
S_0: Concentration of picrate (5×10^{-5} mol dm^{-3}).
1: Cell length(0.1 dm).
ΔA: Change of absorbance at 340 nm.

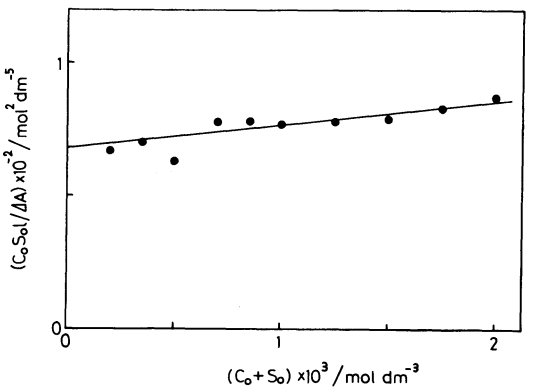


Fig. 3. Benesi–Hildebrand plot for the complex formation between ANS and **1**: pH 6.3(0.1 mol dm^{-3} $NaHPO_4$–0.1 mol dm^{-3} NaH_2PO_4 buffer); 25 °C. The concentration of ANS is 1×10^{-6} mol dm^{-3}. The excitation wavelength is 365 nm and the emission wavelength is 480 nm.
C_0: Concentration of **1**.
S_0: Concentration of ANS(1×10^{-6} mol dm^{-3}).
1: Cell length(0.1 dm).
ΔA: Change of relative fluorescence intensity.

Table 1. Dissociation Constants of Complexes between Cyclophanes(**1**, **2**, **3**) and Substrates[a]

Cyclophane	Dissociation constant(10^3K_d) mol dm^{-3}	
	Picrate	ANS
1	2.0	8.0
2	1.0	5.7
3	0.25	0.31

a) pH 6.3 (0.1 mol dm^{-3} Na_2HPO_4 - 0.1 mol dm^{-3} NaH_2PO_4 buffer), 25 °C.

Table 2. Pseudo-First-Order Rate Constant (k) for the Hydrolysis of p-NPH[a]

Cyclophane	$[N_3^-]\times10^2$	$k\times10^2$	$(\Delta k/C)\times10^{-2}$[b]
	mol dm^{-3}	min^{-1}	min^{-1} mol^{-1} dm^3
None	0	0.13	
None	1	1.6	
1(1×10^{-3} mol dm^{-3})	1	1.7	1
2(1×10^{-3} mol dm^{-3})	1	1.7	1
3(5×10^{-5} mol dm^{-3})	1	1.8	40
3(1×10^{-4} mol dm^{-3})	1	2.1	50

a) pH 8.1 (0.05 mol dm^{-3} NaH_2PO_4-0.025 mol dm^{-3} $Na_2B_4O_7$ buffer), μ=0.1(KCl), 32 °C. b) Increase in the k value per mol dm^{-3} cyclophane.

Hildebrand plot for **1**. The determined K_d values are summarized in Table 1. Here, as in the case of picrate, **1** and **2** form relatively stable complexes with ANS, although **3** forms a much more stable complex with ANS than **1** and **2**. The relative deficiency of the stability for the complexes with **1** and **2** seems to be ascribed to the inefficient hydrophobicity provided by the shorter alkyl chains. The hydrophobicity of the cyclophane-skeleton seems to give an important effect on the complex formation in the case of **1** and **2** in comparison with the case of **3**.

The hydrolyses of active esters have been widely studied as catalyzed by enzyme-mimetic compounds or systems. Various cyclophanes have been used as enzyme models in the hydrolyses of active esters.[1,2,5,8] In the present study, the hydrolysis of p-nitrophenyl hexanoate (p-NPH) in the presence of the cyclophanes (**1**, **2**, and **3**) and azide ion(N_3^-) was investigated. Under the present experimental conditions, the cyclophanes may attract p-NPH by a hydrophobic interaction and N_3^- by an electrostatic force. The reaction followed the pseudo-first-order kinetics until the conversion of ca. 70%, although the rate enhancement was not so large. The pseudo-first-order rate constants (k) are shown in Table 2. In the presence of N_3^- (1×10^{-2} mol dm^{-3}) and **1** or **2** (1×10^{-3} mol dm^{-3}), k was increased by ca. 6% as compared with that in the presence of only N_3^-. In the case of **3**, the increase in the k value per mol dm^{-3} cyclophane ($\Delta k/C$) was much larger than in the cases of **1** and **2**. The strong binding ability of **3** toward p-NPH may be responsible for the larger rate acceleration. The enhancement was, however, not so significant as a whole, probably owing to the poor ability of **3** to bind N_3^-.

In the present study, tetraoxotetraazaparacyclophanes with shorter alkyl chains (**1** and **2**) and the one with relatively long alkyl chains (**3**) have been characterized. As a result, **1** and **2** have been found to include the hydrophobic anionic compounds (picrate and ANS), whereas the binding ability of **1** and **2** is not so large as that of **3**. These cyclophanes enhanced the hydrolysis of p-NPH to a minor extent.

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