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pH-Responsive Molecular Recognition by a Water-soluble Cyclophane Bearing L-Aspartate Moieties

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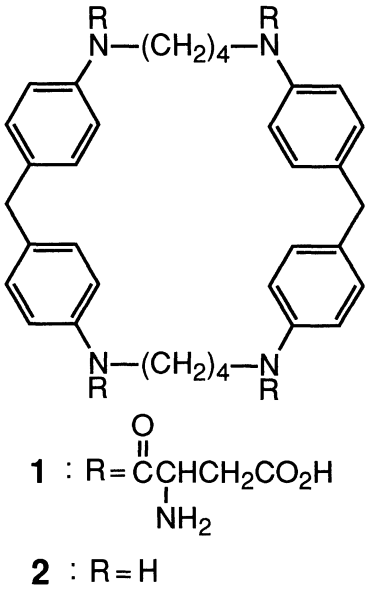
A novel water-soluble cyclophane host bearing four pH-sensitive tentacles was prepared from 1,6,20,25-tetraaza[6.1.6.1]paracyclophane and L-aspartic acid. The host was found to exist primarily as tetracationic and tetraanionic species in pH ranges below 1 and above 11, respectively, and to exhibit pH-responsive molecular recognition toward various aromatic guests.

Cyclophanes having a sizable internal cavity have been employed as basic skeletons for construction of artificial receptors exhibiting excellent molecular recognition in aqueous media.[1-3] While many water-soluble cyclophane derivatives have been prepared up to the present time, there are only a limited number of examples of intelligent hosts having ability to control guest recognition in response to microenvironmental changes or external stimuli.[4,5]

We now designed and synthesized a novel pH-responsive cyclophane (**1**), which is constructed with four L-aspartate moieties as pH-sensitive tentacles and a 1,6,20,25-tetraaza[6.1.6.1]paracyclophane (**2**) ring. In this communication, we are to report on the protonation behavior of **1** and its consequence in molecular recognition ability.



Host **1** was prepared by condensation of **2**[6] with N^{α}-(t-butoxycarbonyl)-L-aspartic acid β-benzyl ester in the presence of dicyclohexylcarbodiimide, followed by removal of the protecting groups.[7] Host **1** is soluble in aqueous media over a wide pH range. First, we examined protonation equilibria of **1** in D_2O at 50.0 °C by means of ^1H NMR spectroscopy (270 MHz). While ^1H chemical shifts for the macrocyclic skeleton were independent of pD, α- and β-proton resonances of the aspartate moiety exhibited marked pD-dependency (Fig. 1). Each of the pD titration curves for the α- and β-protons shows two inflections consistent with

the following pK values; pK_1 = 3.35, pK_2 = 9.29. Judging from the extents and directions of chemical shift changes in these titration curves, it is evident that the β-carboxylic acid and the α-ammonio groups of each aspartate moiety undergo acid dissociation equilibria as schematically shown in Scheme 1; **1** acts primarily as tetracationic and tetraanionic species in pD ranges below 1 and above 11, respectively. The apparent stepwise equilibria suggest that the aspartate moieties are spatially separated by the rigid macrocyclic skeleton and behave independently without mutual interaction in the course of acid dissociation equilibria. Such a state of affairs seems to be reasonable in the light of minimum energy conformations for host **1** in the gas phase, as obtained on the basis of molecular

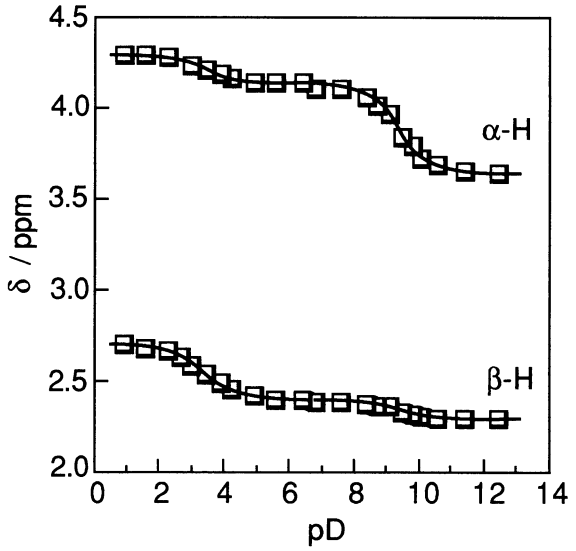
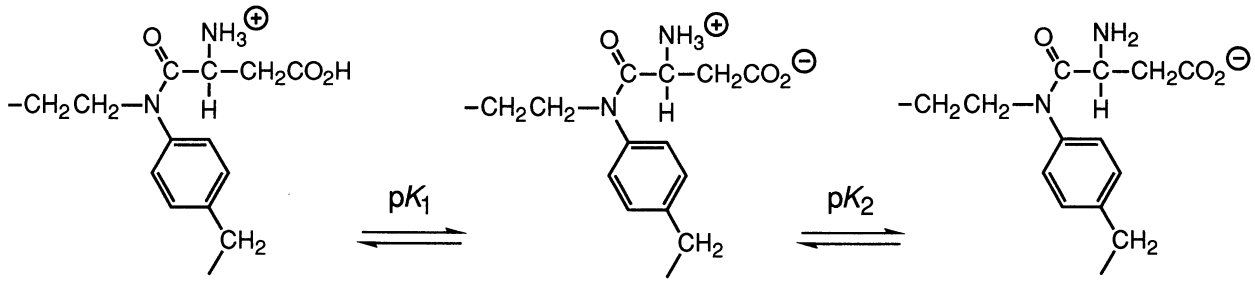


Fig. 1. Correlations between pD and chemical shifts for α- and β-proton resonances of the aspartate moiety of **1** (5.0 mol dm^{-3}) in D_2O at 50.0 °C. Solid lines refer to the calculated data by the aid of evaluated pK values.



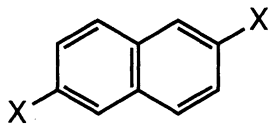
Scheme 1.

mechanics and dynamics (BIOGRAF, Dreiding-I and Dreiding-II[8]) calculations on an IRIS-4D/220GTX workstation (Silicon Graphics). The calculated minimum energy conformations indicate 10–12 Å separation between the neighboring aspartate residues.

Second, we examined guest-binding behavior of **1** as tetracationic and tetraanionic hosts by ^{1}H NMR spectroscopy in aqueous media at 50.0 °C. The following five guests were chosen in order to evaluate a pD-responsive guest recognition ability of **1**; naphthalene-2,6-disulfonate (**3**), 2,6-bis(trimethylammoniomethyl)naphthalene (**4**), 1,4-bis(trimethylammoniomethyl)benzene (**5**), 3-indolylacetic acid (**6**), and 3-(2-aminoethyl)indole (**7**). Upon addition of the host to an aqueous solution of each guest, all the guest signals were subjected to substantial upfield shifts, except for **5** at pD 1.0, reflecting formation of the host–guest complexes.[6] The measurements were carried out in a concentration range from 0.2 to 20 mmol dm^{-3} for **1**, while the concentration of each guest was maintained at 5.0 mmol dm^{-3}. The formation constants (K) for host–guest complexes in

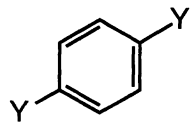
1:1 stoichiometry and the complexation-induced shifts (CIS), the shifts of NMR signals for the guests upon 100% complexation, were evaluated from the ^{1}H NMR titration curves by means of the numerical curve-fitting method in a manner similar to that reported previously.[9,10] The results are listed in Table 1.

The guest-binding ability of **1** is largely dependent on medium pH for all the guest molecules employed here. As for the anionic guest (**3**), the K value at pD 1.0 is much larger than that at pD 11.0. The opposite pH-responsive binding was observed for the cationic guests (**4** and **5**). These results clearly indicate that the host recognizes various guests through different modes of electrostatic interactions that are dependent on medium pH. In addition, the larger K

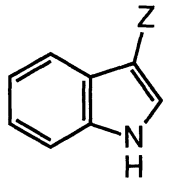


3 : X = SO_3^-

4 : X = $CH_2N^+(CH_3)_3$



5 : Y = $CH_2N^+(CH_3)_3$



6 : Z = CH_2CO_2H

7 : Z = $CH_2CH_2NH_2$

Table 1. Formation constants (K), free energies of complexation (ΔG), and complexation-induced shifts (CIS) for host–guest complexes of **1** with various guests in D_2O at 50.0 °C

Guest	K / dm^3 mol^{-1} ($-\Delta G$ / kJ mol^{-1}) [a]		−CIS / ppm [b]	
	pD = 1.0	pD = 11.0		
3	3500	120	1-H, 5-H	1.60
	(21.9)	(12.8)	3-H, 7-H	0.95
			4-H, 8-H	2.71
4	10	800	1-H, 5-H	1.06
	(6.2)	(17.9)	3-H, 7-H	0.52
			4-H, 8-H	1.62
5	___ [c]	300	Ar-H	0.13
		(15.3)		
6	210	8	2-H	0.69
	(14.4)	(5.6)	4-H	1.45
			5-H	0.84
			6-H	0.64
			7-H	0.93
			α-H	0.48
7	17	220	2-H	0.95
	(7.6)	(14.5)	4-H	1.49
			5-H	0.55
			6-H	0.40
			7-H	0.65
			α-H	0.57
			β-H	0.57

a) $-\Delta G$ values are in parentheses. b) The CIS values at pD 1.0 were identical with those at pD 11.0. c) Complex formation was not detected.

values for the naphthalene derivative (**4**), in comparison with that for the less hydrophobic benzene analogue (**5**), indicate undoubtedly that a hydrophobic effect also contributes much to the enhancement of host–guest complexation. Odashima et al. reported that cyclophane host **2** in its protonated state formed an inclusion complex with 2,7-dihydroxynaphthalene in aqueous media, and that the long axis of the naphthalene ring penetrates the hydrophobic host cavity in an oblique manner (i.e., assuming a pseudoaxial inclusion geometry) on the basis of chemical shift changes for the guest upon complexation.[11] The CIS values obtained for guests **3** and **4** are consistent with formation of the inclusion complexes in which these guests are incorporated into the host cavity in pseudoaxial geometries, and that such geometries remain unchanged regardless of the protonation state of the tentacles, L-aspartate residues. Moreover, the present host exhibited pH-responsive molecular recognition toward a plant hormone (**6**) and its precursor (**7**), although the pH-dependent binding behavior of these guests is opposite to each other. The CIS values for these guests also clearly point out that the guests are truly included in the host cavity, excluding a possibility of undergoing a contact-type interaction with the host.

In conclusion, it now becomes apparent that host **1** exhibits marked pH-responsive molecular recognition toward various organic guests. On this ground, host **1** is expected to be utilized as an excellent pH-responsive carrier in various membrane systems as effective for water-soluble organic molecules. Complete evaluation of the pH-dependent molecular recognition ability of the present host is now in progress in our laboratories.

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