INCLUSION COMPLEX FORMATION BETWEEN A NOVEL ANIONIC CYCLOPHANE AND CATIONIC AROMATIC GUESTS IN AQUEOUS SOLUTION[1]

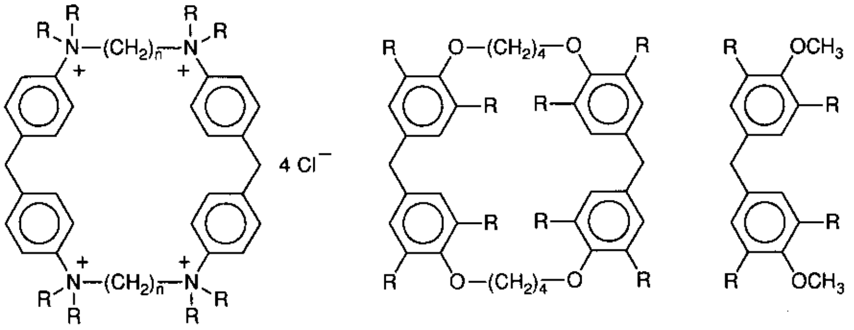
Muneharu Miyake,[a] Makoto Kirisawa,[a] and Kenji Koga[b*]
College of Pharmacy, Nihon University,[a] Narashinodai, Funabashi-shi, Chiba 274, Japan and Faculty of Pharmaceutical Sciences, University of Tokyo,[b] Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract- ^{1}H-Nmr spectral studies have shown that a negatively charged cyclophane (**2**) having eight carboxylate groups that are bonded directly on the aromatic rings forms 1:1 inclusion complexes selectively with positively charged aromatic comounds as guests in alkaline water.

Substrate selectivity in complex formation is one of the goals in host-guest chemistry. Considering that selective complex formation is based on the fit between the host and the guest at the complexed state, it is important to study systematically substrate-selective inclusion of organic guest molecules by artificial host molecules having an inclusion cavity of definite shape, size, and structure.

We have previously reported that cationic cyclophanes (**1**) form 1:1 inclusion complexes with anionic and neutral aromatic guests in particular geometries in aqueous solution.[2,3] These cyclophanes are heteromacrocycles composed from two diphenylmethane units and two bridging chains that are connected *via* four cationic nitrogens, and form hydrophobic cavities of definite shape and size at the complexed states determined by X-ray[2a,i] and ^{1}H-nmr[2b] analysis. Since charge interactions in addition to hydrophobic interactions between the host and the guest are evaluated to be operating for complex formation,[2,3] we expected that cyclophanes having negative charges near their cavities should work as hosts selectively for cationic guests. Based on the fact that cationic cyclophanes (**1**) provide cavities by the face conformation in which all aromatic rings are perpendicular to the macrocyclic ring,[2a,j] introduction of negatively charged substituents on the aromatic rings should not interfere the expected cavities at the face conformation. A D_2-symmetric anionic cyclophane (**3**) designed and synthesized for this purpose[4] has two diphenylmethane units and two tetramethylene bridges that are connected *via* four oxygens, and has eight carboxyl goups directly bonded on the aromatic rings as shown. An acyclic compound (**5**) was prepared from the known **6**,[4] and was used as a reference. In KOD-D_2O solution, **3** and **5** are expected to exist as **2** and **4**, respectively.[5] This paper describes that **2** works as a host selectively for cationic aromatic guests.[6]

Scheme 1



1 R = H, Me; n ≥ 4

2 R = $CO_2^-K^+$
3 R = CO_2H

4 R = $CO_2^-K^+$
5 R = CO_2H
6 R = CO_2Me

For studying inclusion complex formation between a cyclophane as a host and an aromatic compound as a guest in solution, ^{1}H-nmr spectroscopy is the method of choice,[2b] because inclusion of the aromatic guest into the cyclophane cavity can be unequivocally demonstrated by a strong shielding effect due to the aromatic ring(s) of the other component of the complex. In the present study, ^{1}H-nmr spectral examinations were made on the complex formation of **2** and **4** with cationic (**7**, **8**,[7] **9**,[8] **10**,[9] **11**[10]), anionic (**12**), and neutral (**13**) aromatic guests in KOD-D_2O (pD >12.5) below the critical micelle concentration (CMC) of **2**.

It is shown that, by using **2** as a host, marked upfield shifts[11] were observed for the protons of **7**~**11**, while only small changes (less than 0.2 ppm) were observed for those of **12** and **13**. This means that **2** works as a host selectively for cationic aromatic guests. It is also shown that only small changes (less than 0.2 ppm) were induced for the protons of all aromatic compounds (**7**~**13**) examined in the presence of **4** under the same condition.

As an example, proton nmr spectra of (a) **7**, (b) **2**, (c) a mixture of **7** and **2**, (d) **4**, and (e) a mixture of **7** and **4** are shown in Figure 1. In Figure 1c, signals of the protons at C-1, C-3, and C-4 of **7** are shifted upfield[11] in the magnitudes of 1.20, 0.52, and 1.12 ppm, respectively, while as in Figure 1e, chemical shift changes of the same

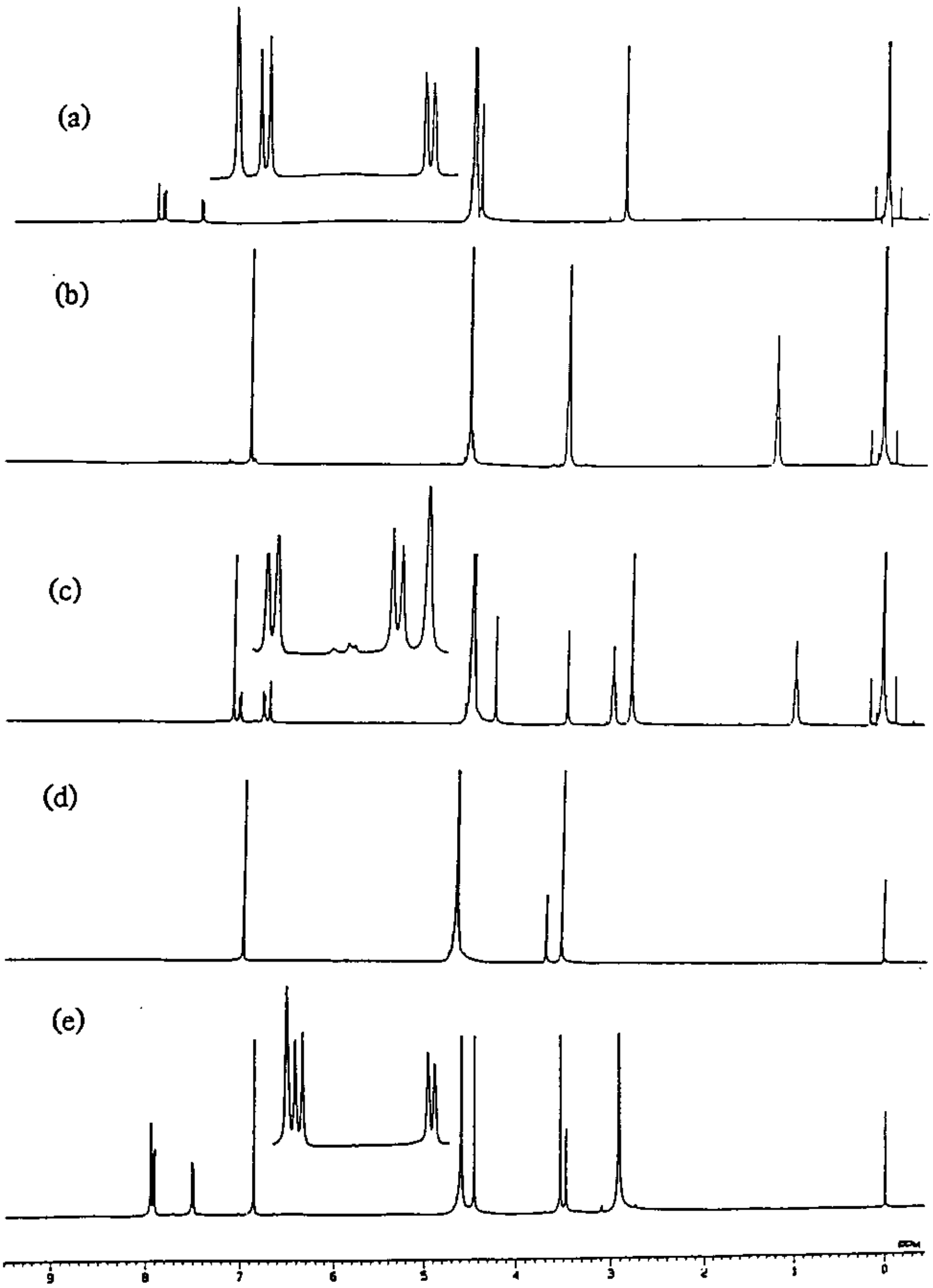
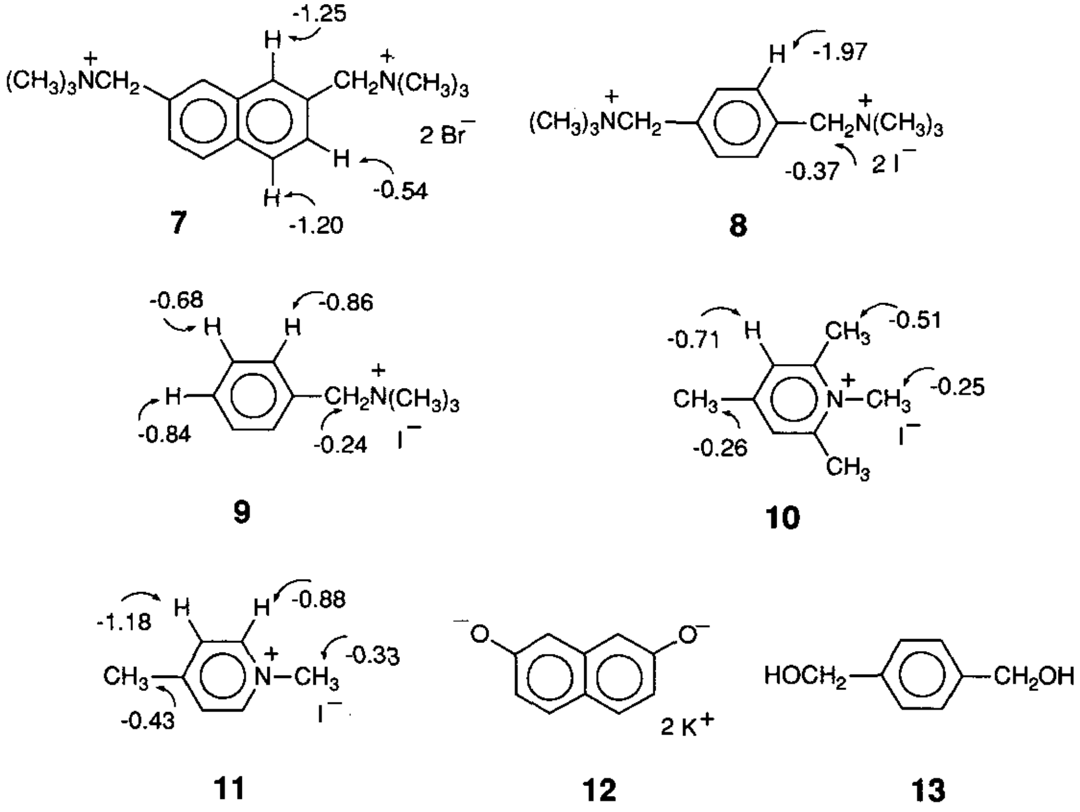


Figure 1. ^{1}H-Nmr spectra of (a) 1.0 x 10^{-2} M **7**, (b) 1.0 x 10^{-2} M **2**, (c) 1.0 x 10^{-2} M each of **7** and **2**, (d) 1.0 x 10^{-2} M **4**, and (e) 1.0 x 10^{-2} M each of **7** and **4** in KOD-D_2O (pD >12.5)

protons of **7** are within experimental errors (0.05, 0.08, and 0.07 ppm, respectively) under the condition shown. Marked upfield shifts can be ascribable to intermolecular shielding effect, and give proof of the formation of a 1:1 inclusion complex.[2b] The magnitudes of Δδ values[12] are dependent on the ratio of the host to the guest. Maximum values ($\Delta\delta_{max}$[12]) of cationic aromatic guests (**7**~**11**) using **2** as a host is shown in Scheme 2. Stability constants (Ks) of the complexes were calculated by Benesi-Hildebrand plot,[13] using the host-induced upfield shifts of the guest proton signals.

Scheme 2 [a]



[a] Values with an arrow indicate $\Delta\delta_{max}$.

By complex formation, each proton signals of the guest shifted in a different degree as shown in Scheme 2. This phenomenon is general using cyclophanes as hosts,[3] and indicates the formation of the complexes in a particular geometry. In the case of **2·7** complex, Δδ values of the protons at C-1 and C-4 of **7** shifted upfield in a similar extent, while that of the proton at C-3 shifted upfield in much smaller extent. This pattern is quite similar to that found for the complex between **1** (R=H, n=4) and 2,7-dihydroxynaphthalene in acidic water.[2b]

This means that the shape and size of the cavity of **2** in alkaline water is quite similar to those of **1** (R=H, n=4) in acidic water at the complexed states, and that the difference in the ability betweeen **1** (R=H, n=4) and **2** as hosts comes from the difference in charges at the periphery of the cavities.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a JASCO IRA-1 infrared spectrophotometer. ^{1}H-Nmr spectra were recorded on a JEOL JNM-GSX 400 Fourier transform nmr spectrometer, or a JEOL JNX-EX 90 Fourier transform nmr spectrometer, using tetramethylsilane as an external standard in KOD-D_2O (pD >12.5). Coupling constants (J) are given in hertz. Mass spectra were recorded on a JEOL JMS-SX 102A mass spectrometer.

5,5'-Methylenebis[2-methoxy-1,3-benzenedicarboxylic acid] (5) A mixture of **6**[4] (0.285 g, 0.62 mmol) in 5N KOH-MeOH (12 ml, 60 mmol), MeOH (30 ml), and H_2O (30 ml) was heated under reflux for 4 h. After concentration to almost a half volume, the resulting solution was acidified by addition of 1N HCl under ice-cooling. Colorless precipitates deposited were collected by filtration, washed with H_2O, and dried *in vacuo*. Recrystallization from MeOH-H_2O gave **5** (0.20 g, 80%) as a colorless powder of mp 264-266°C. Ir (KBr) cm^{-1}: 1727. ^{1}H-Nmr δ: 3.85 (6H, s, OC*H*$_3$), 4.01 (2H, s, Ar-C*H*$_2$-Ar), 7.28 (4H, s, Ar-*H*). Mass m/z: 405 (M^++1). *Anal.*Calcd for $C_{19}H_{16}O_{10}$: C, 56.44; H, 3.99. Found: C, 56.18; H, 4.03.

N,N,N,N',N',N'-Hexamethyl-2,7-naphthalanedimethanaminium Dibromide (7) A solution of 2,7-bis(bromomethyl)naphthalene (0.157 g, 0.5 mmol) in 28% aqueous trimethylamine (2.5 ml, 11.1 mmol) and MeOH (2.0 ml) was heated under reflux for 18 h. Evaporation *in vacuo* to dryness gave a solid, which was recrystallized from MeOH-AcOEt to give **7** (0.21 g, 93%) as colorless prisms of mp 296°C (decomp.). ^{1}H-Nmr δ: 2.87 (18H, s, N-C*H*$_3$), 4.40 (4H, s, Ar-C*H*$_2$N), 7.43 (2H, dd, J=8.4 and 1.2, C_3-*H*, C_6-*H*), 7.84 (2H, d, J=8.4, C_4-*H*, C_5-*H*), 7.90 (2H, d, J=1.2, C_1-*H*, C_8-*H*). *Anal.* Calcd for $C_{18}H_{28}N_2Br_2$: C, 50.02; H, 6.53; N, 6.48 Found: C, 49.99; H, 6.51; N, 6.47.

N,N,N,N',N',N'-Hexamethyl-1,4-benzenedimethanaminium Diiodide (8) Colorless needles of mp >300°C (reported mp 298-300°C,[7a] mp 316-317°C (decomp.)[7b]). ^{1}H-Nmr δ: 3.23 (18H, s, N-C*H*$_3$), 4.67 (4H, s, Ar-C*H*$_2$N), 7.80 (4H, s, Ar-*H*).

N,N,N-Trimethylbenzenemethanaminium Iodide (9) Colorless needles of mp 179-180°C (reported mp 180°C[8]). ^{1}H-Nmr δ: 3.10 (9H, s, N-C*H*$_3$), 4.50 (2H, s, Ar-C*H*$_2$N), 7.57 (5H, s, Ar-*H*).

1,2,4,6-Tetramethylpyridinium Iodide (10) Colorless prisms of mp 206°C (reported mp 204°C[9]). ^{1}H-Nmr δ: 2.49 (3H, s, C_4-CH_3), 2.71 (6H, s, C_2-CH_3, C_6-CH_3), 3.98 (3H, s, N-CH_3), 7.53 (2H, s, C_3-H, C_5-H).

1,4-Dimethylpyridinium Iodide (11) Colorless prisms of mp 143-144°C (reported mp 143-145°C[10]). ^{1}H-Nmr δ: 2.58 (3H, s, C4-CH_3), 4.29 (3H, s, N-CH_3), 7.82 (2H, d, J=6.6, C_3-H, C_5-H), 8.56 (2H, d, J=6.6, C_2-H, C_6-H).

CMC Measurement ^{1}H-Nmr spectra of the solutions of **3** in KOD-D_2O (pD >12.5) were measured. Chemical shifts of all the protons did not change in concentration range of **3** from 1.25 x 10^{-3} M to 8.0 x 10^{-2} M (8 points).

Determination of Ks Values of the Complexes The Ks values of the host-guest complexes were determined by ^{1}H-nmr spectra using the host-induced upfield shifts of the guest proton signals in KOD-D_2O (pD >12.5), on the basis of the Benesi-Hildebrand equation.[12] The concentration of the guests (**7**-**11**) was 1.0 x 10^{-2} M, while those of the host (**2**) ranges from 2.5 x 10^{-3} M to 3.0 x 10^{-2} M (5 points). The non-linear curve fitting procedure with the least squares method was applied.[14] The Ks values of the complexes with **2** thus obtained are as follows. **7**: 5.8 x 10^4 M^{-1}; **8**: 3.5 x 10^3 M^{-1}; **9**: 0.9 x 10^3 M^{-1}; **10**: 2.0 x 10^3 M^{-1}; **11**: 1.4 x 10^3 M^{-1}.

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11. Since the system is in the nmr chemical shift fast exchange limit, the proton signals of the guest appear at the average of the chemical shifts of the free guest and those of the complexed guest, weighed by the fractional population of the guest in each environment.
12. $\Delta\delta = \delta$(host + guest) - δ(host or guest only). Maximum value ($\Delta\delta_{max}$) is the calculated value of $\Delta\delta$ where the concentration of the host or the guest is infinite. Negative values of $\Delta\delta$ indicate upfield shifts.
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14. The program was devised by Dr. Akiko Itai, Faculty of Pharmaceutical Sciences, University of Tokyo.

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