structure, so that the number of the allowed (stable) conformations is limited to a great extent. As a result, **1** seems to show no change in its conformation even in a CTC matrix. On the other hand, 1-(1-naphthyl)propanes and 1-(2-naphthyl)propanes show "flexible" structures and seem to be able to change their shapes (conformations) in accord with the shape of the interacting counterpart (CTC) in the diasteromeric complexes. Figure 12 shows the conformational energy maps of the (*R*)- and (*S*)-isomers of **1**, **8**, and **19** as a function of ϕ_1 and ϕ_2 where the maps for the relevant isomers are superimposed for each molecule. Of particular note is that in **1** the two isomers show no overlap in the allowed conformation, while in **8** a partial overlap is recognized, and in **19** the two isomers are nearly completely overlapped in the stable conformation. Thus, **19** may be assumed as a "soft" substrate, against which the chiral discrimination was inefficient. The present study has demonstrated that the optical resolution may be interpreted at least partly in tems of the "rigid" and "soft" concept.

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Spectroscopic Studies on Exchange Properties in Through-Ring Cyclodextrin Complexes of Carbazole–Viologen Linked Compounds: Effects of Spacer Chain Length[1]

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Analysis of ^{1}H NMR spectra (400 MHz) revealed a novel mode of interaction between cyclodextrin (CD) and carbazole–viologen linked compounds (CAC*n*V), where the spacer chain was consisted of *n* methylene units (*n* = 4, 6, 8, 10, and 12). In the case of α-CD, the complexed species lived long enough to afford distinct proton signals, when the spacer chain was relatively long (*n* ≥ 8). As to CAC12V, the equilibrium constant for the 1:1 complex was 4.9×10^4 M^{-1} at 30 °C and coalescence temperatures for the proton signals exceeded 100 °C. Clear NOEs were observed to prove strong interaction between the protons in the CD cavity and the spacer methylene groups of CAC12V. The spacer was concluded to be encased in the cavity of α-CD. In the case of β-CD, essentially the same "through-ring CD complex" was formed. The line shape analysis indicated that the free energies of activation at 70 °C for complexation and decomplexation were 11.6 and 17.2 kcal/mol, respectively. Activation parameters for the α-CD complexes were evaluated by the rate of disappearance of intramolecular charge-transfer absorption (420 nm) on the addition of α-CD. The free energy of activation for decomplexation was found to exceed 22 kcal/mol in the α-CD complexes for CAC*n*V (*n* = 8, 10, and 12). The viologen moiety of CAC*n*V was concluded to be the site of entrance for forming "through-ring CD complex", and the large activation energies were ascribed to dehydration of viologen units to go through the CD cavity.

Introduction

Incorporation of hydrophobic compounds into the inner cavity of cyclodextrin (abbreviated to CD) has been reported in an enormous number of papers. The guest molecules generally possess an aromatic moiety, which fits in the cavity of CD.[2] Bimodal inclusion behaviors are also expected when the structure of the guest molecules consisted of an aromatic and an aliphatic moiety. Cyclodextrins preferentially include the aromatic moieties rather than the linear alkyl chains. The affinity of alkyl groups approaches that of phenyl groups, however, if a bulky moiety such as a *tert*-butyl group is present in the structure.[3] Aliphatic amphiphiles have also been known to form CD complexes. The typical examples are carboxylic acids[4] and viologen derivatives,[5] where the aliphatic tails are suggested to sit in the CD cavity. None of these CD complexes has been found to be stable enough to afford distinct NMR signals due to the complexed species.[6] Rapid exchange between the complexes and free species are taking place on an NMR time scale so that time-averaged signals are detected. Recently, novel CD complexes were discovered to afford distinct NMR signals apart from free species.[7] The first example was phenothiazine–viologen linked compounds complexed with either α- or β-CD.[8] The ionic head group was suggested to go through the inner pore of CD. This novel inclusion mode of CD

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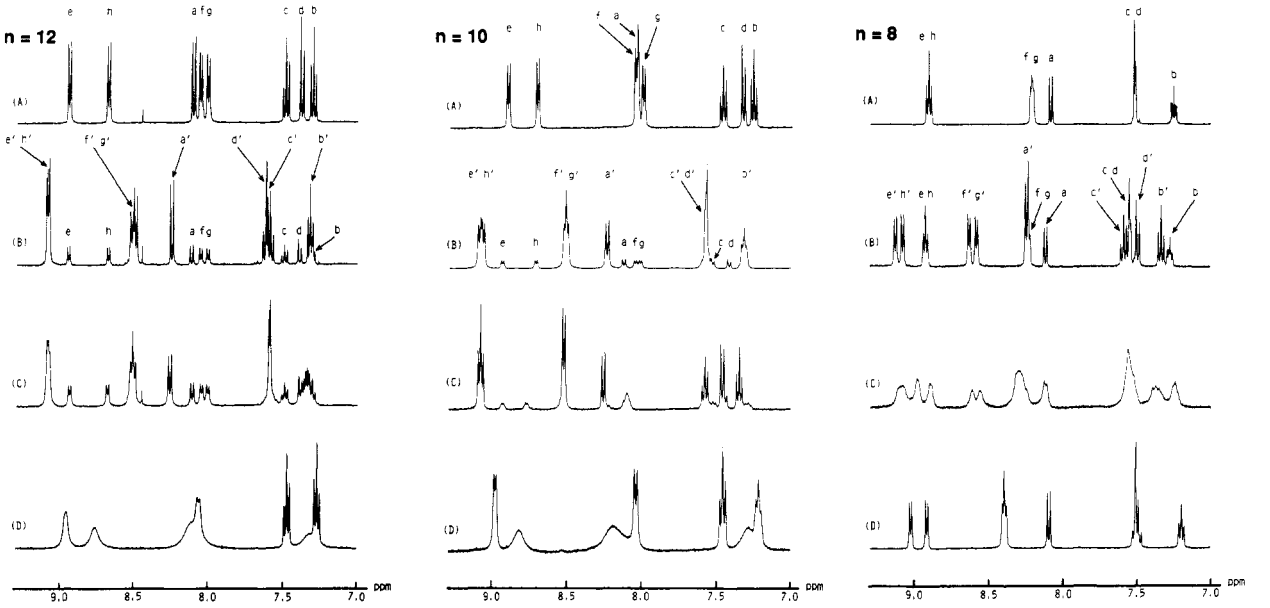
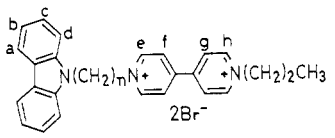
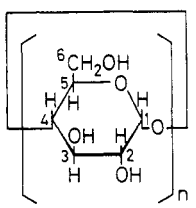


Figure 1. Effects of CD on the ^{1}H NMR spectra of aromatic moieties in CAC*n*V (n = 12, 10, and 8) in D_2O at 30 °C: (A) without CD, (B) with α-CD, (C) with β-CD, and (D) with γ-CD. Assignments a–h were made as shown in A, and the corresponding signals in the complexed species were indicated by the same letters with a prime. The CD concentrations were equimolar to those of CAC*n*V in solution: CAC12V (0.4 mM), CAC10V (2 mM), and CAC8V (2 mM).

complex was soon verified by the use of polymethylenebis(1-pyridinium) as the guest molecule.[9] The NMR spectra indicated that electromagnetic microenvironment of the originally equivalent protons in the spacer is brought into a pair of asymmetric situations on the complex formation. A rotaxane-type structure[10] was assigned to the complex, where α-CD was suggested to encase the spacer chain. Dynamic behaviors of the novel rotaxane-type CD complexes have not been well characterized yet. Then, NMR spectra of the following carbazole–viologen linked compounds were studied in detail to elucidate dynamics of the through-ring CD complexes.



CACnV (n=4,6,8,10,12)



n = 6 : α-CD
n = 7 : β-CD
n = 8 : γ-CD

Experimental Section

The linked compounds were obtained by coupling 9-(ω-bromoalkyl)carbazole and 1-propyl-4,4′-bipyridinium bromide. Guaranteed reagent-grade CD from the following commercial sources were used without further purification: α- and β-CD from Tokyo Kasei Kogyo Co., Ltd., and γ-CD from Wako Pure Chemical Industries, Ltd. Electronic absorption spectra were recorded by a Shimadzu UV-240 instrument. Proton NMR spectra (400 MHz, D_2O solution) were measured by the use of a JEOL Model JNM-GSX 400 spectrometer. The sample solution contained the linked compounds and CD in a 1:1 molar ratio at the concentration specified in each figure caption. The sample concentrations (0.4–1 mM) were kept below critical micellar concentration (1.6 mM for CAC12V, for example) so that no aggregation of the solute took place in the aqueous solutions. The chemical shifts were measured by the use of an external DSS standard in a sealed capillary tube.

Results and Discussion

(1) Assignment of ^{1}H NMR Spectra of the CD Complexes. The ^{1}H NMR spectra for the linked compounds with three different spacer chain lengths (CAC*n*V; n = 12, 10, and 8) are summarized in Figure 1. As to the linked compound with a longer spacer ($n \geq 8$), distinct signals due to the stable α-CD complexes were clearly observed at lower field with respect to those of free species. The assignments were made by the aid of COSY and NOE techniques. In the case of CAC12V, for example, unique assignment of alkyl protons (i–m, n–p) is possible on the basis of COSY spectrum shown in Figure 2a. Alternative choices still remain in the assignments of proton signals both in carbazole moiety (a, c, d, b or d, b, a, c) and in viologen moiety (e, h, f, g or h, e, g, f) as denoted in the order of increasing fields. In the NOESY spectrum of the same compound (Figure 2b), intramolecular NOEs were observed between the following pairs: e and m, h and n, and d and i. On the basis of these observations, one arrives at unique assignments of viologen moiety (e, h, f, g) and carbazole moiety (a, c, d, b) as denoted in the order of increasing fields. The signals due to the complexed species for CAC12V-α-CD system were analogously assigned by the aid of COSY and NOE spectra. The signal intensities of the complexed species increased with the α-CD concentration. The equilibrium constant for the 1:1 complex, as evaluated from the integrated signal intensities, was 4.9×10^4 M^{-1} at 30 °C.

Essentially the same behavior was observed with CAC12V-β-CD system: distinct signals due to the complexed species were detected apart from the free species. The signal intensities afforded an equilibrium constant of the β-CD complex (1.5×10^4 M^{-1}), which is somewhat less than that for the α-CD complex at the same conditions. On the addition of γ-CD, the viologen and carbazole proton signals of CAC12V changed their shape and chemical shifts, but no distinct signals due to the complexed species were separately observed. It is clear that the complexed species in CAC12V-γ-CD system are rapidly exchanging with free species under the investigated conditions. All of these NMR spectroscopic features are very much the same as observed with the corresponding phenothiazine–viologen linked compound.[8]

(2) Effects of Spacer Chain Length on the Complexation Behaviors. As to α-CD, the distinct signals due to the complex were clearly observed down to CAC8V (Figure 1). On the other hand, the ^{1}H NMR signals for CAC6V and CAC4V were hardly af-

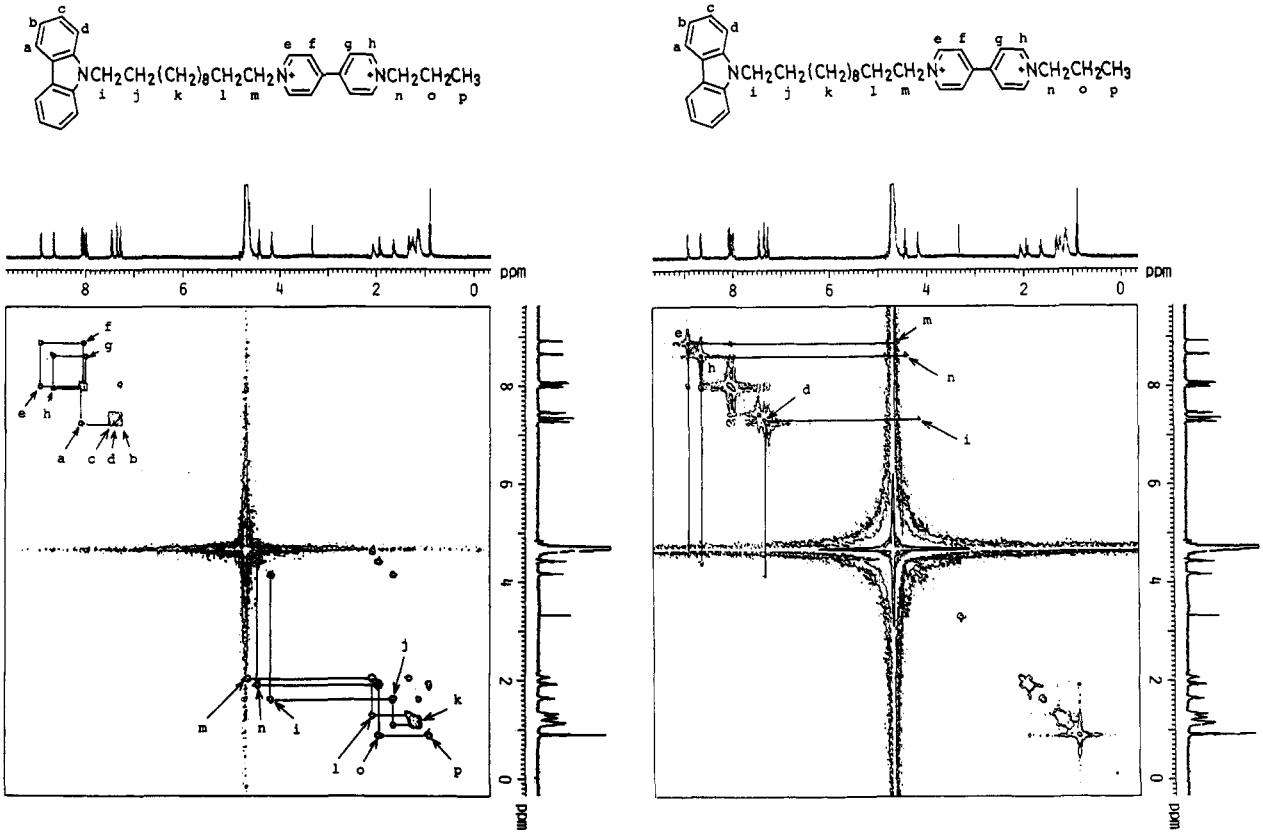


Figure 2. Two-dimensional NMR spectra for CAC12V (0.6 mM) in D_2O at 30 °C: (a, left) COSY and (b, right) NOESY spectra.

TABLE I: Induced Chemical Shifts ($\Delta\nu$, Hz) Due to Complex Formation between CAC12V (0.4 mM) and α-CD (0.4 mM) in D_2O at 30 °C

proton position	$\Delta\nu^a$	proton position	$\Delta\nu^a$
a	58	e	61
b	8	f	174
c	57	g	205
d	84	h	161

$^a \Delta\nu = \nu_{\text{with } \alpha\text{-CD}} - \nu_{\text{without } \alpha\text{-CD}}$.

fected by α-CD. The interaction between α-CD and the linked compounds thus rapidly decreased with the decrease of the spacer chain length.

In the case of β-CD, the rate of exchange between the complex and the free species clearly increased at CAC8V as observed with the rather broad signal shapes in Figure 1. For the linked compounds with shorter spacer chain (n = 6 and 4), no distinct signals due to the complexed species were observed anymore. The chemical shifts of the proton in the aromatic moieties were affected, however, by the addition of β-CD, which indicated rapid exchange between the complex and free species.

The rapid exchange limit prevailed up to n = 8 in the case of the γ-CD complexes (Figure 1). At the longer spacer chain length, the exchange rate gradually decreased as indicated by broadening of signal shapes. No separate signals due to the stable complexes were observed, however, in the investigated spacer chain length at 30 °C.

The induced chemical shifts due to complexation between CAC12V and α-CD are listed in Table I. Remarkably large downfield shifts (ca. 200 Hz) were noticed with a viologen proton (g). In the case of the rotaxane-type complex with polymethylenebis(1-pyridinium),[9] the chemical shifts of originally equivalent protons were split into an asymmetric pair. The chemical shift separation for the pair of protons at the central part of the spacer was considerably larger than those for the pairs at the end of the spacer. Then, the complex-induced chemical shift could be ascribed to electric field gradient in the cyclodextrin cavity.[11] At least one component of the pair of signals was observed at lower field with respect to the free species, but the

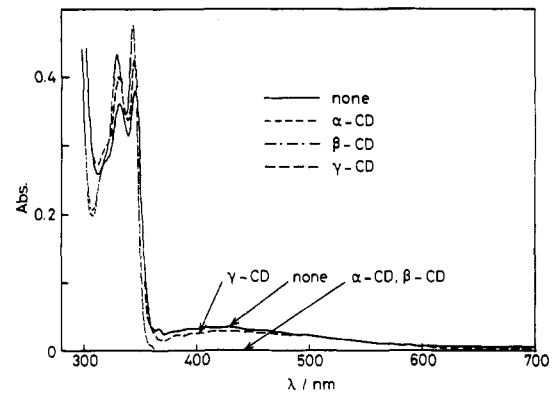


Figure 3. Effects of CD (2 mM) on the charge-transfer absorption of CAC12V (0.1 mM) in aqueous solution at room temperature.

downfield shift did not exceed 40 Hz.[9] Thus, it is obvious that some new factors should be taken into consideration to account for the large, complex-induced chemical shifts in Table I. One of the important characteristics of carbazole–viologen linked compounds is the fact that a concentration-independent, charge-transfer absorption band was observed (λ_{max}, ca. 420 nm for CAC12V; Figure 3) with the free species. The absorption band completely disappeared on the addition of either α- or β-CD. The charge-transfer absorption band remained unaffected, however, on the addition of γ-CD. This peculiar behavior of the γ-CD system will be discussed at the end of this paper.

The above spectroscopic observations with α- or β-CD are reasonably explained by conformational change in the linked compound, as shown in the following scheme, on going from free species into the through-ring complexes. Both the low-field shifts for the aromatic protons of CAC12V and the high-field shifts for α-CD may be ascribed to change in the anisotropic effects of diamagnetic susceptibilities of neighboring group (carbazole or viologen unit) on the complexation. The suggested conformational change is also in good agreement with the fact that a charge-transfer band was observed with free species but not with the stable CD complex. Some electronic factors associated with the

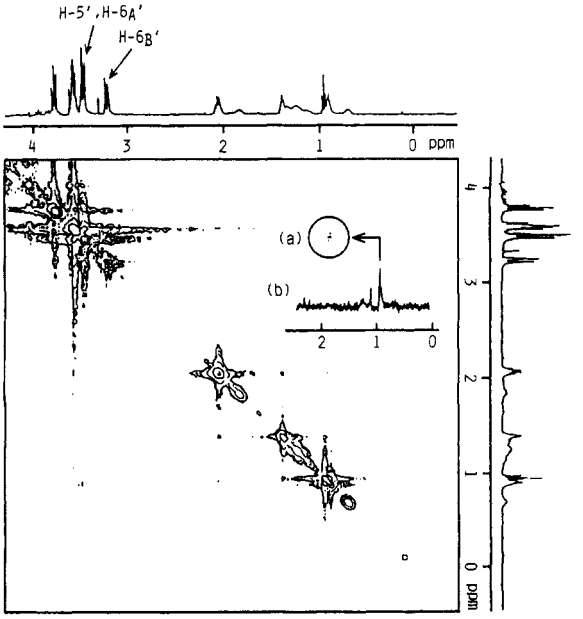


Figure 4. A NOESY spectrum for α-CD (1 mM)/CAC12V (1 mM) complex in D_2O at 30 °C. The outstanding signals, as denoted by a, indicate the interaction between CD proton (H-5′ and/or H-6_A′) and the spacer protons located at the central part of the methylene chain. The NOE difference spectrum is given by the inset b, where H-5′ and H-6_A′ at 3.502 ppm were irradiated.

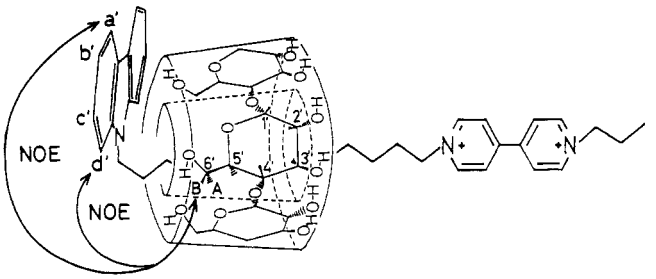
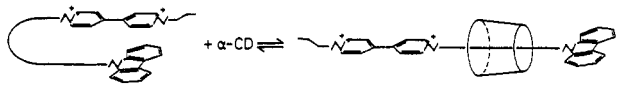


Figure 5. The most possible structure of complexation between CAC12V and α-CD.

SCHEME I



charge-transfer complex might be partly responsible for the remarkable downfield shifts of viologen groups in CAC12V.

The suggested structure of the stable CAC12V–α-CD complex was further supported by careful examination of chemical shifts of the aliphatic proton signals and NOE as shown in Figure 4. The signals due to H-5′ and H-6′ of α-CD were appreciably shifted to higher fields on complexation with CAC12V. The H-6′ signals were split into an AB-type quartet, which indicated a large difference in the magnetic environment ($\Delta\nu$ = 102 Hz) for the two geminal protons (H-6_A′ and H-6_B′) of α-CD cavity. Three NOE cross peaks were observed between the inner proton (H-5′ and/or H-6_A′) and the spacer methylene of CAC12V (Figure 4a). In addition, NOE difference spectra clearly indicated the presence of interaction between the protons in the CD cavity (H-5′ and/or H-6_A′) and the spacer methylene of CAC12V (Figure 4b). The difference NOE experiments also indicated that the carbazole moiety is interacting with the outer surface of α-CD: NOEs were detected between the outer proton (H-6_B′) and carbazole protons (a′ and d′). The results suggested that the methylene group at the 6′-position of α-CD was covered with carbazole moiety. All of these data strongly suggest the following through-ring model as the most possible form of complexation between CAC12V and α-CD (Figure 5).

The natures of through-ring complexes were further elucidated by examining effects of the spacer chain length on the charge-transfer band and chemical shifts of the viologen protons in the absence of CD. As to CAC6V and CAC8V, the intensity of the charge transfer band was only 40% of those observed with other members of the investigated linked compounds (Table II). The charge-transfer absorption for CAC4V recovered to almost the same intensity as that for CAC12V. In contrast to the case of CAC12V, however, the charge-transfer bands did not disappear even in the presence of α-CD.

TABLE II: Effects of the Spacer Chain Length (n) on Charge-Transfer Absorption Intensity at 420 nm for CACnV (0.4 mM) in Aqueous Solutions at 30 °C

n	abs	n	abs
4	0.096	12	0.077
6	0.037	12	0.103
8	0.036		

TABLE III: Effects of the Spacer Chain Length (n) on the Difference in Chemical Shifts ($\Delta\nu$, Hz) between e and h Protons Observed in D_2O at 30 °C

n	$\Delta\nu^a$	n	$\Delta\nu^a$
4	−261	10	80
6	−139	12	107
8	7		

$^a\ \Delta\nu = \nu_h - \nu_e$.

The absolute value of chemical-shift difference ($\Delta\nu$) between e and h protons for the uncomplexed CACnV also decreased with the increase of the spacer chain length (n = 4 and 6), reached a minimum at n = 8, and increased again at longer chain length (n = 10 and 12) as summarized in Table III. This interesting observation is ascribed to the fact that the signals for e and h protons were shifted to mutually opposite direction as the spacer chain length was increased: low-field shifts for e proton, and high-field shifts for h proton. Similar trends were also observed with the chemical shifts for f and g protons. The diamagnetic anisotropy effects of carbazole moiety on the chemical shifts of the viologen protons are clearly changing with the spacer chain length.

In the stable CD complex, however, the signals for e and h protons were always observed at ca. 9.1 ppm irrespective of the chain length (n = 12, 10, and 8; Figure 1). The chain-length dependence of both the charge-transfer absorption and the chemical-shift difference may be best described as due to variation in conformational equilibria between an open, extended conformer and a bent form required for face-to-face interaction of the terminal groups (carbazole and viologen units).

The face-to-face interaction may be favored in the linked compounds with either a short (n = 4) or a longer spacer (n = 10 and 12), but not with a medium-size spacer (n = 6 and 8). Formation of through-ring CD complexes forces the spacer chain to take the open, extended conformations so that the face-to-face interactions are suppressed in the linked compounds with a relatively longer spacer (n = 8, 10, and 12).

(3) Thermodynamic Parameters for the Complexation and the Decomplexation Process. Appreciable temperature effects on the ^1H NMR signal shapes were observed with CAC12V in the presence of β-CD (Figure 6a). The ring proton signals of the viologen units (e′ and h′) reached the coalescence point at ca. 70 °C. No indication of coalescence was detected up to 90 °C, however, with CAC12V in combination with α-CD (Figure 6b). The small radius of the cavity in α-CD apparently hinders dissociation of the complexed species more strongly than the case of β-CD.

In order to elucidate dynamic properties of the through-ring CD complexes, thermodynamic parameters for the most stable complexes with α-CD were carefully evaluated. The equilibrium constants at various temperatures (30–90 °C) were obtained from the ratio of integrated intensities of proton signals of viologen moiety (e and h) for free and complexed species. The thermodynamic parameters for the complexation, as summarized in Table IV, indicate that the through-ring complex gets stabilized with

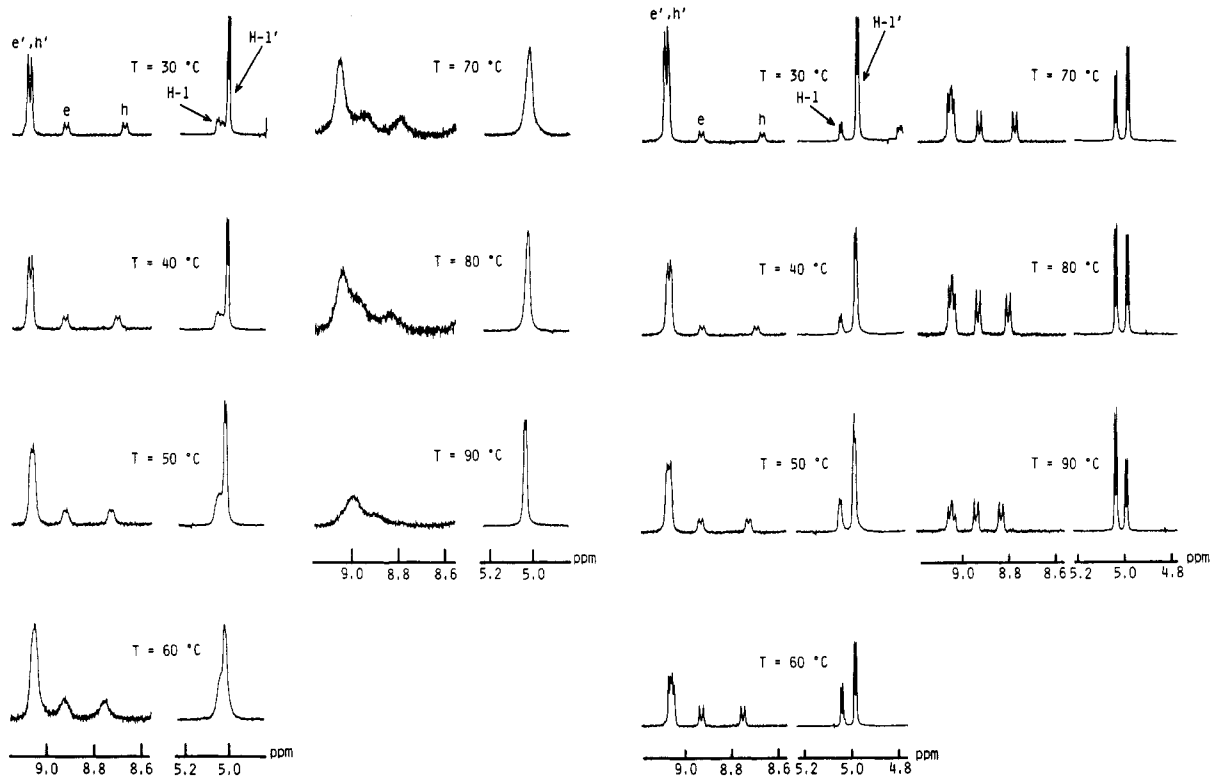


Figure 6. Temperature effects on the line shape for viologen protons (e, h) and H-1 signals of the CD (1 mM)–CAC12V (1 mM) system in D_2O: (a, left) β-CD and (b, right) α-CD.

TABLE IV: Effects of the Spacer Chain Length (n) on the Thermodynamic Parameters for Complex Formation between CACnV (n = 8, 10, 12) and α-CD

n	ΔG^a	ΔH^b	ΔS^c	$\Delta G^{\neq a}$	$\Delta H^{\neq b}$	$\Delta S^{\neq c}$
8	−4.6 ± 0.1	−13.0 ± 0.5	−27.4 ± 1.6	18.0 ± 0.1	7.1 ± 0.5	−36.1 ± 3.0
10	−5.8 ± 0.1	−13.0 ± 0.4	−23.2 ± 1.1	18.0 ± 0.2	8.4 ± 0.2	−31.8 ± 2.0
12	−6.5 ± 0.1	−13.5 ± 0.3	−23.0 ± 1.0	17.6 ± 0.1	11.9 ± 0.3	−19.0 ± 2.0

[a] Units = kcal/mol (303 K). [b] Units = kcal/mol. [c] Units = cal/mol·K.

the increase of the spacer chain length. The entropy term appears to be dominant in spacer chain length effect on stabilization of the through-ring CD complex.

The activation parameters for the complex formation were obtained from the rate of disappearance of the charge-transfer bands (420 nm) on the addition of α-CD. Experimental conditions[12] were adjusted so that the rate followed pseudo-first-order reaction kinetics. The measurements were made at seven different temperatures (10–45 °C) to obtain the enthalpy and entropy of activation. The thermodynamic parameters, as summarized in Table IV, afforded a reaction profile for the formation of the through-ring CD complexation and the decomplexation process shown in Figure 7. The free energy of activation for the decomplexation process exceeded 22 kcal/mol in each case. The value is in good agreement with the previously discussed temperature effects on the signal shapes of through-ring α-CD complexes.

In the case of β-CD complex of CAC12V, three proton signals at 1-position of β-CD were observed near 5 ppm. The three signals were assigned to free species (H-1), minor complex species, and major complex species (H-1′) as denoted in the order of increasing field. The minor species corresponding to another 1:1 complex species was assigned to the stereoisomer due to the orientation of β-CD ring. The contribution of the minor complex was ca. 7% at 30 °C and decreased at high temperatures. The line-shape analyses at the coalescence point (70 °C) were carried out by taking the contributions of the protons at 1-position of CD (H-1 and H-1′) into consideration. The line-shape simulation indicated that the free energies of activation for complexation and decomplexation were 11.6 and 17.2 kcal/mol, respectively. The difference in barrier height between the complexation and decomplexation processes (−5.6 kcal/mol) is in good agreement with

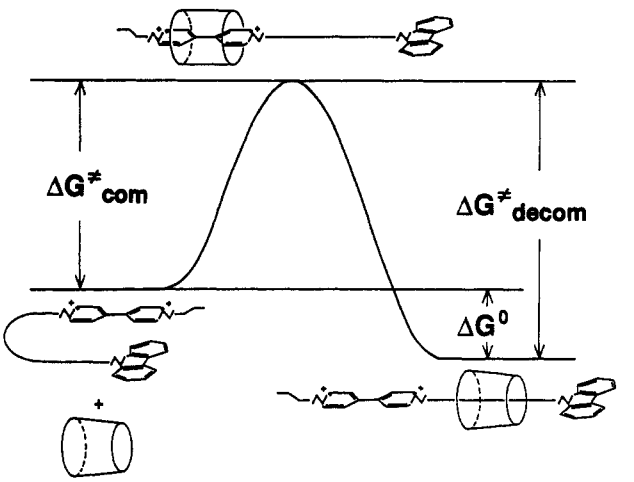


Figure 7. Schematic presentation of the reaction profile for formation of the through-ring CD complex and decomplexation process.

the free energy change in complexation (−5.6 kcal/mol) as evaluated from the equilibrium constant ($K = 3.6 \times 10^3$ M^{-1}) by the use of integrated signal intensity for viologen protons (e and h).

The free energy of activation for complexation is markedly less than that for the corresponding α-CD complex. As a consequence, the rate of complexation was too fast to be followed by the measurement of fading charge-transfer band just after addition of β-CD into CAC12V solution. As to the equilibrium constants and free energy change in the complexation of CAC12V, no discernible difference between α-CD ($K = 4.9 \times 10^4$ M^{-1} and ΔG

= −6.5 kcal/mol) and β-CD ($K = 1.5 \times 10^4$ M^{-1} and $\Delta G = -5.8$ kcal/mol) was noticed at 303 K. It is clear that the free energy change in the complexation can account for only a minor part of the activation energy for the decomplexation process. In other words, the activation process for decomplexation must be understood as a barrier penetration problem for viologen to go through the CD pore.

The pore size of CD will be the dominant factor in determining the barrier penetration rate. In the case of α-CD, the space-filling model indicates that even a naked viologen unit induces some distortion of the CD ring to be penetrated. Dehydration of the viologen unit is inevitable for the barrier penetration.

In agreement with this reasoning, a fairly good isokinetic relationship could be observed between the enthalpies and entropies of activation for CAC*n*V (n = 8, 10, and 12).

As to the β-CD, the pore size is large enough to let the naked viologen penetrate the ring with ease. The appreciably large barrier for the decomplexation ($\Delta G^{\ddagger} = 17.2$ kcal/mol as previously explained in the section of line-shape analysis of ^{1}H NMR spectra) then indicates that the activation energy must be used to dehydrate the viologen unit.

No difficulty is expected for the hydrated viologen unit to get in and out of the γ-CD cavity, since the entrance is as wide as 8.5 Å in diameter even in the narrower side of the pore. In agreement with this expectation, no distinct signals for the stable complexes were separately observed with CAC*n*V in the presence of γ-CD.

One should recall the fact that the intensity of charge-transfer absorption band of CAC12V was unaffected by the presence of γ-CD. There are several possible models to explain this interesting phenomenon.

One of the simplest models will be rapid reduction of the equilibrium constant for the through-ring complex on going from β-CD to γ-CD. The through-ring CD complex should clearly suppress the charge-transfer band even under rapid exchange limit, if the population of the complexed species exceeds 5% of the carbazole–viologen linked compounds in the solution. In order to suppress the contribution of the through-ring complex below 1% under the experimental conditions, the equilibrium constant for the complexation should be less than 10^2 M^{-1}. The value corresponds to reduction by 2 orders of magnitude in the equilibrium constant on going from β- to γ-CD, which seems to be rather extraordinary. It should be also worth mentioning that the charge-transfer band was hardly affected by 20-fold increase of γ-CD concentration.

An alternative model will be simultaneous incorporation of carbazole and viologen moieties to the same γ-CD. There are several precedents for simultaneous incorporation of two chromophores in the big cavity of γ-CD molecule.[13] Formation of charge-transfer complexes was also noticed when electron donors with a naphthalene moiety and electron acceptors with polynitrobenzene units were simultaneously incorporated into the γ-CD cavity.[14]

All of these data strongly indicate that the simultaneous incorporation model is more appropriate to account for the present situation. In agreement with this suggestion, a circular dichroism peak was clearly detected at the wavelength region the charge-transfer absorption band of CAC12V in the presence of γ-CD. Elaborate studies are further required to elucidate dynamic behavior of the γ-CD complex in details.

Conclusion

Stable "through-ring CD complexes" were formed with a relatively long polymethylene spacer ($n \geq 8$). By the aid of COSY and NOE techniques, the spacer was confirmed to be encased in the cavity of α-CD. The thermodynamic parameters indicated that activation processes for complexation and decomplexation could be explained as a barrier penetration problem for the viologen moiety. In order to get into the hydrophobic inside of the CD cavity, the viologen moiety appears to be dehydrated in the activation process. The stable through-ring CD complex was obtained only if the viologen moiety was attached to a spacer with considerable chain length ($n \geq 8$). The reason may be that the dehydrated viologen with the long spacer completely passes through the hydrophobic pore and gets fully hydrated again at the other side of CD.

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Registry No. CAC4V–α-CD, 141484-72-2; CAC6V–α-CD, 141484-73-3; CAC8V–α-CD, 141484-66-4; CAC10V–α-CD, 141484-68-6; CAC12V–α-CD, 141484-63-1; CAC12V–β-CD, 141484-64-2; CAC4V, 141484-69-7; CAC6V, 141484-70-0; CAC8V, 141484-65-3; CAC10V, 141484-71-1; CAC12V, 141484-62-0; 1-propyl-4,4′-bipyridinium bromide, 39127-06-5.

Supplementary Material Available: NMR and NOE data (11 pages). Ordering information is given on any current masthead page.

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