Characterization of the β-Cyclodextrin Inclusion Complexes with Bichromophoric 1-Benzyloxy-2-pyridone and Related Compounds

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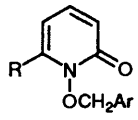
The 1:1 complexation behaviour of β-cyclodextrin (β-CDx) with the title compounds has been investigated by measuring UV absorption, circular dichroism (CD) and ^{1}H NMR spectra of the β-CDx inclusion complexes formed. A methyl substituent introduced into the pyridone moiety of bichromophoric 1-benzyloxy-2-pyridone (**1**) was found to affect greatly the guest conformation within the cavity as well as the **1**–β-CDx-complex stability. On the other hand, in addition to the inclusion-complex stability, the pyridone-ring conformation in the β-CDx complexes with 1-(1-naphthyl)methyloxy-2-pyridone (**3**) and its positional isomer, 1-(2-naphthyl)methyloxy-2-pyridone (**5**), does not undergo any methyl-substituent effects. An analysis of the induced CD bands originating from the naphthyl and pyridone residues of **3** and **5** revealed that the substitution mode of a naphthyl group, axially incorporated into the cavity, exerts dramatic effects both on the orientation of a planar pyridone ring to the cavity axis and on the stability of the obtained complex. Remarkable differences in guest conformation and inclusion-complex stability between the **3**–β-CDx and **5**–β-CDx systems were interpreted in terms of positional isomer effects caused by the preferential axial immersion of both 1-naphthyl and 2-naphthyl groups into the cavity. The NMR data substantiate the structure of the β-CDx complexes with **1** and its methyl derivative where both the phenyl and pyridone chromophores are situated inside the cavity, whereas the pyridone ring in the β-CDx complexes with **3** and **5** was shown by these data to be located around the rim of the secondary hydroxy-group side.

Cyclodextrins (CDxs) are water-soluble cyclic oligosaccharides composed of six (α-CDx), seven (β-CDx) and eight (γ-CDx) D-(+)-glucopyranose units having approximate inner-cavity diameters of 5.7, 7.8 and 9.5 Å, respectively, and depths of 7.8 Å.[1] The hydrophobic internal cavity of CDxs has an ability to incorporate hydrophobic organic compounds in aqueous solution, provided that the sizes of the host's internal cavity and the entering guest molecule are suitable for complexation. This ability has made it possible to utilize CDxs for many applications.[1,2] CDxs have recently been shown to induce conformational enantiomerism of bichromophoric dinaphthylmethane derivatives.[3] It has been proposed that a steric factor in the guest–host inclusion complex dominates the observed enantioselectivity.

In the course of systematic investigations regarding the excited-state behaviour and reactivities of 1-hydroxy-2-pyridone, having a significant antibacterial activity,[4] and its derivatives, we have found that bichromophoric 1-benzyloxy-2-pyridones undergo the N–O bond cleavage from higher vibrational states of the first excited singlet state to give 2-pyridones and benzaldehyde as the main products.[5] We thought that it would be of importance to control this intriguing excited-state reactivity of cyclic hydroxamic acid derivatives by accommodating these guest molecules into the CDx cavity. Since bichromophoric molecules are expected to exhibit an interesting complexation behaviour with CDxs,[3,6] we first embarked on a detailed study of the structure and stability of inclusion complexes formed between β-CDx and 1-arylmethyloxy-2-pyridones **1**–**6** in aqueous solution containing 4% (v/v) methanol which is added to increase the solubility of these compounds. The problem of primary concern is whether structural differences in the aryl group among **1**–**6** exert pronounced effects on the structure and stability of the inclusion complexes produced. In this paper we present results which demonstrate that the guest molecules **1**–**6** form 1:1 inclusion complexes with β-CDx in which the orientation of the pyridone ring to the CDx cavity axis is dramatically affected not only by the axial immersion of naphthyl groups of **3** and **5** into the cavity, but also by the introduction of a methyl group into **1**.



1 R = H, Ar = Ph
2 R = Me, Ar = Ph
3 R = H, Ar = 1-naphthyl
4 R = Me, Ar = 1-naphthyl
5 R = H, Ar = 2-naphthyl
6 R = Me, Ar = 2-naphthyl

Results and Discussion

UV Absorption and Circular Dichroism (CD) Spectra of **1** *and* **2**.—Fig. 1 shows absorption and CD spectra of **1** in 4% (v/v) MeOH–H_2O containing β-CDx. With a progressive increase in the β-CDx concentration (0.15–1.5 × 10^{-2} mol dm^{-3}), an absorption band at 297 nm originating from the pyridone chromophore is slightly red-shifted (2–3 nm) with a decrease in its intensity, accompanied by isosbestic points at 228, 253 and 305 nm. This observation suggests the formation of a 1:1 inclusion complex of β-CDx with **1**. Interestingly, the distinct induced circular dichroism (ICD) of positive sign, although it is weak, was observed in the first absorption band. The coupled oscillator theory developed by Kirkwood and Tinoco[7] predicts that the guest electronic transition polarized perpendicular to the CDx cavity axis exhibits a negative ICD sign while that polarized parallel to the axis gives a positive ICD sign.[8] Taking into account that the first absorption transition of the 2-pyridone moiety at 297 nm is polarized along the C^3–C^6 axis of this planar ring,[9] application of this rule to the **1**–β-CDx system

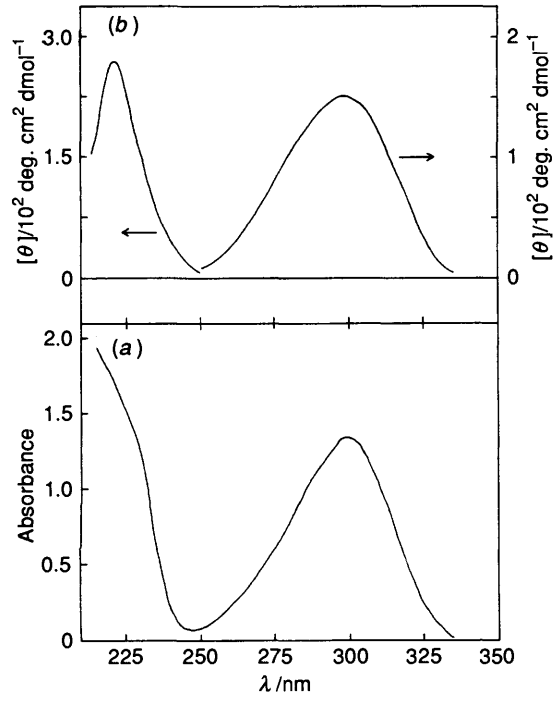


Fig. 1 UV absorption (*a*) and CD (*b*) spectra of **1** (2.0×10^{-4} mol dm^{-3}) in the presence of β-CDx (1.5×10^{-2} mol dm^{-3}) in 4% (v/v) MeOH–H_2O

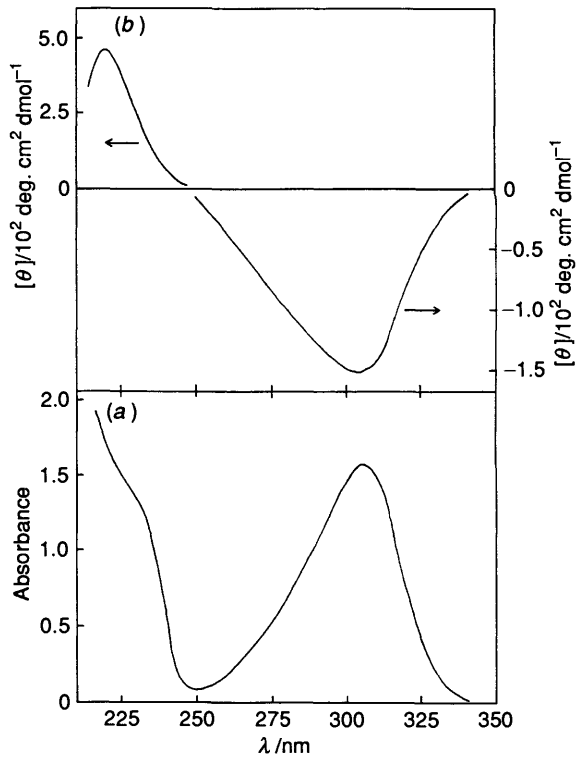


Fig. 2 UV absorption (*a*) and CD (*b*) spectra of **2** (2.0×10^{-4} mol dm^{-3}) in the presence of β-CDx (1.5×10^{-2} mol dm^{-3}) in 4% (v/v) MeOH–H_2O

allows us to conclude that the C^3–C^6 axis in the β-CDx complex is approximately parallel to the cavity axis. The **1**–β-CDx complex also gives a weak positive ICD curve in the 210–250 nm region. 1-Ethoxy-2-pyridone with a structure corresponding to the pyridone chromophore exhibits two absorption bands at 226 nm (molar absorption coefficient, $\varepsilon_{max} = 7.0 \times 10^3$ mol^{-1} dm^3 cm^{-1}) and 297 nm ($\varepsilon_{max} = 6.9 \times 10^3$ mol^{-1} dm^3 cm^{-1}) in 4% (v/v) MeOH–H_2O, while the absorption bands of benzyl alcohol having a structure corresponding to the phenyl moiety appear at 205 nm ($\varepsilon_{max} = 1.1 \times 10^4$ mol^{-1} dm^3 cm^{-1}) and 257 nm ($\varepsilon_{max} = 190$ mol^{-1} dm^3 cm^{-1}). Because these two chromophores give the second absorption bands with molar absorption coefficients comparable to each other around 220 nm, it is very difficult to determine the benzene-ring orientation to the cavity axis from the sign of the ICD band in the short-wavelength region alone.

As demonstrated in Fig. 2, substitution of a methyl group for hydrogen at the 6-position of the pyridone skeleton exerted dramatic effects on the ICD sign of the pyridone absorption band. The observed ICD band of negative sign at 305 nm reveals that the C^3–C^6 axis of this ring is nearly perpendicular to the cavity axis, if a methyl group affects the direction of transition moment of the 297 nm band to a negligible extent. The finding that varying concentrations of β-CDx ($0.15–1.5 \times 10^{-2}$ mol dm^{-3}) cause the same absorption spectral changes of **2** as those observed for **1** suggests that steric repulsion between the methyl group and the cavity wall and/or the benzene ring brings about a conformational change of the included guest molecule **2**, affording the negative ICD band in the 250–350 nm region.

On the other hand, in addition to negligible absorption spectral changes of **1** and **2** in the presence of α-CDx (1.5×10^{-2} mol dm^{-3}), no circular dichroism was induced at the absorption bands of these guest molecules. Since one generally assumes that the inner width of α-CDx is suitable for taking up the more hydrophobic phenyl part, the less hydrophobic pyridone part might suppress the full inclusion of a phenyl group into this cavity. Although we attempted to analyse the complexation behaviour of β-CDx with **1** and **2** through fluorescence measurements, weak fluorescences of these guests and small changes in their emission intensities with β-CDx made it very difficult to obtain reproducible results.

UV Absorption and CD Spectra of **3–6**.—In order to scrutinize aryl-substituent effects on the structure and the stability of the β-CDx inclusion complex, we prepared 1-(1-naphthyl)methyloxy-2-pyridone (**3**) and its positional isomer, 1-(2-naphthyl)methyloxy-2-pyridone (**5**), along with their methyl derivatives **4** and **6** and investigated the complexation behaviour of β-CDx with **3–6** in 4% (v/v) MeOH–H_2O. As shown in Fig. 3, **3** gave two positive ICD bands at 224 and 302 nm in the presence of β-CDx, while a weak negative ICD band was observed at 278 nm. 1-Naphthalenemethanol, used as a reference compound for the 1-naphthyl moiety of **3**, exhibited the ^1L_a band ($\varepsilon_{max} = 5.9 \times 10^3$ mol^{-1} dm^3 cm^{-1}) with a short-axis-polarized transition moment at 280 nm and the ^1B_b band ($\varepsilon_{max} = 5.8 \times 10^4$ mol^{-1} dm^3 cm^{-1}) with a long-axis-polarized transition moment at 222 nm.[10] Thus, the short-wavelength absorption band at 223 nm [Fig. 3, curve (*a*)] can be considered to consist predominantly of the ^1B_b band, and the long-wavelength one appeared in the 250–350 nm region to be composed of the ^1L_a band of the naphthalene residue and the 297 nm band of the 2-pyridone chromophore. The observations of a negative ICD peak at 278 nm and a positive ICD peak at 224 nm substantiate the axial inclusion of a 1-naphthyl group into the cavity, while the ICD peak of positive sign at 302 nm indicates the parallel orientation (to the cavity axis) of the C^3–C^6 axis in the pyridone ring. The intense positive ICD band at 302 nm of the **3**–β-CDx complex as compared to that of the **1**–β-CDx one [Fig. 1, curve (*b*)] may be due to the very restricted movement of the pyridone moiety within the cavity. An analysis of Fig. 4 reveals that the ICD spectral behaviour of **3** is not subject to methyl-substituent effects, although an ICD peak at 302 nm is slightly red-shifted (5 nm) by the introduced methyl group as in the case of **2** (6 nm). This finding is consistent with there being no serious difference in the guest's

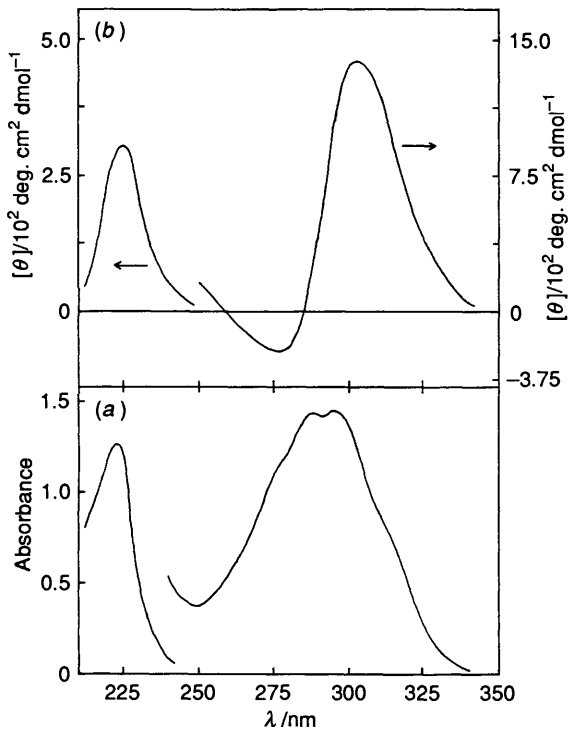


Fig. 3 UV absorption (*a*) and CD (*b*) spectra of **3** at 2.0×10^{-5} mol dm^{-3} (210–250 nm) and 1.5×10^{-4} mol dm^{-3} (250–350 nm) in 1.0×10^{-2} mol dm^{-3} β-CDx aqueous solution containing 4% (v/v) MeOH

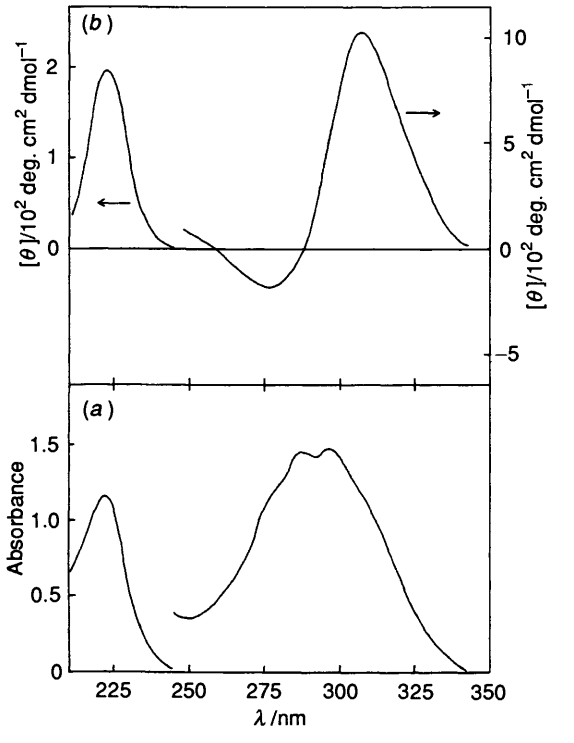


Fig. 4 UV absorption (*a*) and CD (*b*) spectra of **4** at 2.0×10^{-5} mol dm^{-3} (210–250 nm) and 1.5×10^{-4} mol dm^{-3} (250–350 nm) in 1.0×10^{-2} mol dm^{-3} β-CDx aqueous solution containing 4% (v/v) MeOH

conformation between the **3**–β-CDx and **4**–β-CDx inclusion complexes.

In Fig. 5 are shown UV absorption and CD spectra of **5**, with a 2-naphthyl group. A comparison of the absorption spectrum of **5** with that of 2-naphthalenemethanol, which gave the ^1B_b band ($\varepsilon_{max} = 6.1 \times 10^4$ mol^{-1} dm^3 cm^{-1}) at 222 nm and the ^1L_a band ($\varepsilon_{max} = 4.8 \times 10^3$ mol^{-1} dm^3 cm^{-1}) at 274 nm, indicates that the chiral β-CDx cavity produces a positive ICD peak corresponding to the ^1B_b transition of the naphthalene chromophore, and that the sign of the ICD band should be negative over the range of the ^1L_a transition of this chromophore. Thus, a 2-naphthyl group is also accommodated axially into the cavity. Contrary to the **3**–β-CDx complex, a relatively large negative ICD band originating from the first π,π* transition of the pyridone chromophore[9] was observed in the **5**–β-CDx complex, confirming the perpendicular orientation of the C^3–C^6 axis to that of the cavity. A remarkable difference in the pyridone-ring orientation between the **3**–β-CDx and **5**–β-CDx complexes is regarded as being due to positional isomer effects caused by the preferential axial inclusion of both the 1-naphthyl and 2-naphthyl residues. As is evident from Fig. 6, a methyl group introduced into **5** affected the ICD spectral behaviour of this guest to, if any, only a slight extent. If the pyridone moiety is deeply immersed into the cavity along with the naphthyl moiety, a greatly changed ICD pattern must be observed from analogy with the ICD spectra of the guest molecules **1** and **2** in the presence of β-CDx. Negligible effects of a methyl group on the ICD behaviour of 1-naphthylmethyloxy-2-pyridones–β-CDx inclusion complexes are reasonably interpreted in terms of the shallow insertion of the pyridone ring into the cavity.

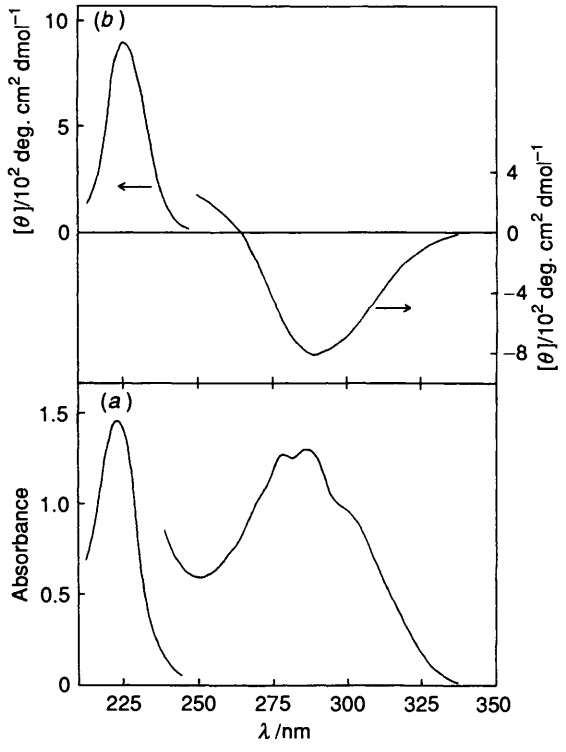


Fig. 5 UV absorption (*a*) and CD (*b*) spectra of 2.0×10^{-5} mol dm^{-3} (210–250 nm) and 1.5×10^{-4} mol dm^{-3} (250–350 nm) of **5** in the presence of β-CDx (1.0×10^{-2} mol dm^{-3}) in 4% (v/v) MeOH–H_2O

Stoichiometry and Equilibrium Constants for β-CDx Inclusion Complexes.—The facts that β-CDx induces UV absorption spectral changes of 1-arylmethyloxy-2-pyridones (APs) accompanied by isosbestic points and that APs exhibit ICD signals in the presence of this cyclodextrin strongly suggest the appearance of the 1 : 1 AP–β-CDx inclusion complex as shown,

$$AP + \beta\text{-CDx} \overset{K}{\rightleftharpoons} AP\text{–}\beta\text{-CDx},$$

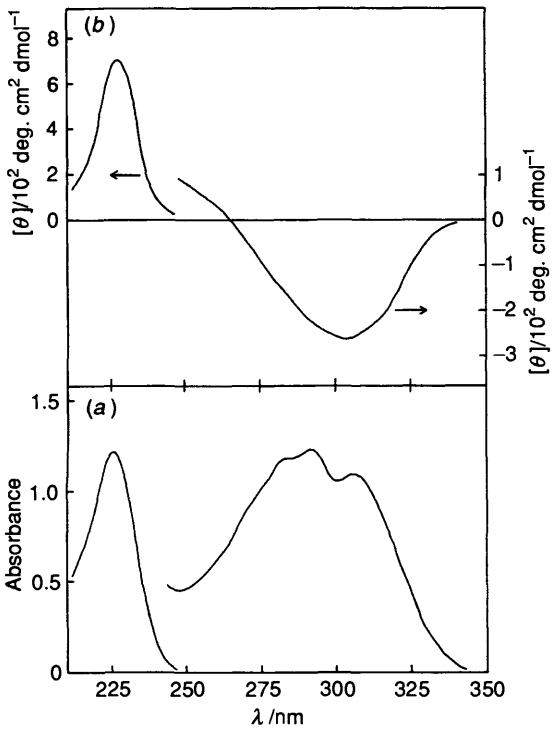


Fig. 6 UV absorption (*a*) and CD (*b*) spectra of 2.0×10^{-5} mol dm^{-3} (210–250 nm) and 1.5×10^{-4} mol dm^{-3} (250–350 nm) of **6** in the presence of β-CDx (1.0×10^{-2} mol dm^{-3}) in 4% (v/v) MeOH–H_2O

where K is the equilibrium constant for formation of the complex. The changes in the absorption (ΔA) and circular dichroism ([θ]) spectra as a function of the β-CDx concentration ([β-CDx]$_0$ ≫ [AP]$_0$, where [β-CDx]$_0$ and [AP]$_0$ refer to the initial concentrations of β-CDx and AP, respectively) can be related to the equilibrium reaction according to eqn. (1), which is frequently utilized as the Benesi–

$$1/\Delta I = 1/a + 1/(aK[\beta\text{-CDx}]_0) \quad (1)$$

Hildebrand expression;[11] where ΔI is ΔA or [θ] and a is the constant at given concentrations of AP and MeOH.

As typically shown in Fig. 7, the observation of a good linear relationship between the reciprocal of ellipticity ($1/[\theta]$) and the reciprocal of [β-CDx]$_0$ establishes the formation of the AP–β-CDx inclusion complex with a 1 : 1 stoichiometry. Similar linear plots were obtained also from the relation between $1/\Delta A$ and $1/[\beta\text{-CDx}]_0$. From the ratio of intercept to slope in these linear plots, the equilibrium constant K was determined and is shown in Table 1. The following facts can be recognized from an inspection of this Table: (*i*) both UV and CD spectroscopic methods give K values comparable to each other; (*ii*) the K value for the complexation of β-CDx with **3** is much smaller than that for the association with **5**; and (*iii*) the introduction of a methyl group into the pyridone ring of **1** increases the K value to some extent, whereas the K values for formation of the **3**–β-CDx and **5**–β-CDx complexes undergo minor methyl-substituent effects.

β-CDx has been shown to accommodate 2-substituted naphthalenes axially and 1-substituted naphthalenes in both axial and equatorial modes into its cavity.[8a] It has been suggested that the steric effect of substituents plays a role of prime importance in inducing such a different inclusion process. Since the deep intracavity inclusion of both the naphthalene and pyridone units is not possible as revealed by the Corey–Pauling–Koltun molecular model, steric hindrance due to the

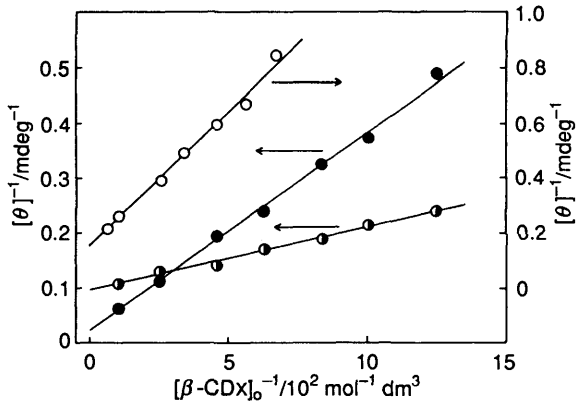


Fig. 7 Benesi–Hildebrand plots of $1/[\theta]$ *vs.* $1/[\beta\text{-CDx}]_0$ for the β-CDx complexation with **1** (○), **3** (●) and **5** (◑)

Table 1 Equilibrium constants (K) for the association of β-CDx with the guests **1**–**6**, obtained by UV and CD spectroscopic methods at 24 ± 1 °C[a]

Guest	K/dm^3 mol^{-1} CD	UV
1	160	170
2	500	450
3	65	90
4	67	80
5	870	1000
6	1000	900

[a] [β-CDx]$_0$ = 0.15–1.5 × 10^{-2} mol dm^{-3} for the complexation with **1** and **2** ([**1**]$_0$ = [**2**]$_0$ = 2.0×10^{-4} mol dm^{-3}) and [β-CDx]$_0$ = 0.10–1.0 × 10^{-2} mol dm^{-3} for the complexation with **3**–**6** ([**3**]$_0$ = [**4**]$_0$ = [**5**]$_0$ = [**6**]$_0$ = 1.5×10^{-4} mol dm^{-3}).

pyridone skeleton of **3** might inhibit the equatorial insertion of a 1-naphthyl group leaving the pyridone moiety around the rim of the β-CDx cavity. Enforced axial inclusion of the 1-naphthyl residue may generate large strain within the **3**–β-CDx complex, thus decreasing the stability of this complex to a considerable extent. The alternative explanation for a pronounced difference in stability between the **3**–β-CDx and **5**–β-CDx systems is the formation of hydrogen bonding between the β-CDx hydroxy groups and the guest molecule **5**, since the pyridone carbonyl oxygen easily forms hydrogen bonds with protic solvents.[12] Negligible methyl-substituent effects on the stability of the β-CDx complexes with **3** and **5** are consistent with the shallow inclusion of the pyridone residue, allowing us to speculate that the guest carbonyl oxygen is still capable of forming a hydrogen bond to the medium in the complex. The hydrogen bonding with the host hydroxy groups is thus unlikely to stabilize the produced inclusion complex to, if any, a large extent. This consideration supports the former interpretation.

β-CDx is supposed to accommodate both the pyridone and phenyl units of **1** into its cavity, as judged by the sizes of the guest and host molecules as well as UV absorption spectral changes of the less hydrophobic pyridone chromophore in the presence of β-CDx. Dramatic changes in the ICD spectra caused by introducing a methyl group into **1** strongly suggest that a conformational change of this guest takes place within the complex owing to steric hindrance of the bulky substituent. This finding, being in contrast with that obtained from methyl-substituent effects on the ICD spectra of **3** and **5**, provides supporting evidence for the deep intracavity immersion of both chromophores of **1**. It is, thus, reasonable to interpret the increased stability of the **2**–β-CDx complex in terms of a more favourable van der Waals contact of **2** with the cavity wall, as compared to the **1**–β-CDx complex.

Table 2 ^{1}H NMR spectral data of the guests **1–3** and **5** (5.0×10^{-3} mol dm^{-3}), obtained in the absence and presence of β-CDx (5.5×10^{-3} mol dm^{-3})

	δ						
System	H^3	H^4	H^5	H^6	Me^6	$ArCH_2$	Ar
1[a]	6.78	7.61	6.40	7.60		5.32	7.49
1–β-CDx[a]	6.80	7.62	6.32	7.39		5.36	7.47
2[a]	6.67	*ca.* 7.54[b]	6.40		2.38	5.31	7.53
2–β-CDx[a]	6.73	7.58	6.33		2.18	5.41	7.48
3[a]	6.79	7.56	6.18	7.21		5.84	*c*
3–β-CDx[a]	6.81	7.54	6.05	6.81		5.85	
5[d]	6.78	7.57	6.26	7.68		5.48	*c*
5–β-CDx[d]	6.82	*e*	6.30	7.74		5.55	

[a] Measured in 4% (v/v) CD_3OD–D_2O. [b] Could not be accurately determined because of overlapping with the phenyl proton signal. [c] It was very difficult to assign the naphthalene-ring proton signals owing to strong overlap of each proton signal. [d] Measured in 20% (v/v) CD_3OD–D_2O. [e] Could not be estimated because of overlapping with the naphthalene-ring proton signals.

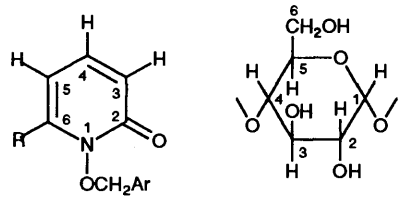
Table 3 ^{1}H NMR spectral data of β-CDx (5.5×10^{-3} mol dm^{-3}), obtained in the absence and presence of the guest **1–3** or **5** (5.0×10^{-3} mol dm^{-3})

	δ					
System	1-H	2-H	3-H	4-H	5-H	6-H
β-CDx[a]	5.11	3.69	4.00	3.62	*ca.* 3.89[b]	3.92
β-CDx–**1**[a]	5.10	3.68	3.92	3.62	3.76	3.88
β-CDx–**2**[a]	5.10	3.69	3.91	3.61	3.76	3.90
β-CDx–**3**[a]	5.10	3.68	3.91	3.62	3.78	3.90
β-CDx[c]	5.10	3.68	3.96	3.62	3.84	3.91
β-CDx–**5**[c]	5.09	3.66	3.92	3.63	3.77	3.89

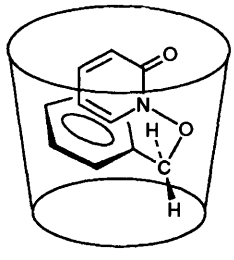
[a] Measured in 4% (v/v) CD_3OD–D_2O. [b] Approximate δ value. See Experimental section. [c] Measured in 20% (v/v) CD_3OD–D_2O.

^{1}H *NMR Spectra of β-CDx Inclusion Complexes.*—In a previous study we have demonstrated that the pyridone-ring proton and benzyl methylene-proton signals are sensitive to ring-current effects of the phenyl group and deshielding effects of the amide carbonyl group in **1**, respectively, and hence chemical shift changes of these protons become a good means for deducing the conformation of this bichromophoric molecule.[5b] In order to obtain more direct evidence for the β-CDx inclusion complex structure, we measured ^{1}H NMR spectra of **1–3** and **5** with and without β-CDx in 4% (v/v) CD_3OD–D_2O (**1–3**) or 20% (v/v) CD_3OD–D_2O (**5**) at 24 ± 1 °C. The lower solubility of **5** forced us to use relatively high concentrations of CD_3OD to determine reliable chemical shifts within the estimated error of ±0.01 ppm. In Table 2 are tabulated the chemical shifts (δ) of the guests with and without β-CDx and the δ values of β-CDx in the presence and absence of each guest molecule are collected in Table 3. We define the change in chemical shift (Δδ/ppm) as the difference in chemical shifts between proton signals of the guest or β-CDx in the absence and presence of β-CDx or the guest, respectively.

β-CDx induces a dramatic upfield shift (Δδ = +0.21) of the H^6 signal of **1**. This upfield shift must be due to ring-current



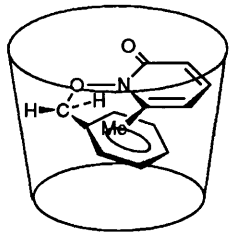
effects of a phenyl group in the guest. There is also a significant upfield shift (Δδ = +0.08) of the H^5 signal, while the H^3, H^4 and methylene proton resonances are only slightly affected in the presence of β-CDx. Since 3-H and 5-H are located at the interior of the cavity, the relatively large upfield shifts (Δδ = +0.08 for 3-H and *ca.* +0.13 for the 5-H) of these proton signals can be ascribed to the deep inclusion of the phenyl moiety into the cavity. Additionally, the resonances for the 1-H, 2-H, 4-H and 6-H protons located at the exterior of the β-CDx torus are relatively unaffected (Δδ = 0 to +0.04) by the addition of the guest **1**, suggesting that the association does not take place at the exterior of the torus. The finding that the H^6 proton is the most favourably situated in the shielding region of the benzene ring in **1** presents additional evidence for the full immersion of both the phenyl and pyridone parts. Taking into account that the C^3–C^6 axis is nearly parallel to the cavity axis, an NMR analysis of the **1**–β-CDx complex allows us to propose the complex structure **I**.



I

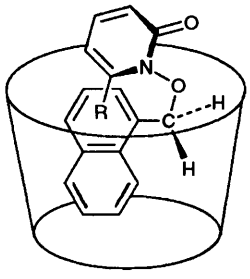
On the other hand, β-CDx induces distinct downfield shifts of the H^3 (Δδ = −0.06), H^4 (*ca.* −0.04) and methylene proton (−0.10) signals of the guest **2**, although upfield shifts of the H^5 (Δδ = +0.07) and methyl (+0.20) proton signals are comparable to those of the corresponding proton signals for the **1**–β-CDx system. The ICD spectrum of the **2**–β-CDx complex clearly indicates that a dramatic conformational change of the guest molecule occurs by introducing a methyl group into **1**. As already suggested, steric repulsion between the methyl substituent and the cavity wall and/or the benzene ring may be responsible for the observed conformational change of the guest **2** in the complex. In order to explain the ICD and ^{1}H NMR spectral behaviour of the **2**–β-CDx system, we propose the complex structure **II** in which a methyl group is placed above the shielding zone of the benzene ring and the benzylic protons approach further the amide carbonyl group of the pyridone moiety, the C^3–C^6 axis of which is approximately perpendicular to the cavity axis. The pronounced downfield shift of the H^3 signal is explained by the placement of this proton in the stronger deshielding region of the benzene ring.

^{1}H NMR spectra with and without **3** show that the 3-H (Δδ = +0.09) and 5-H (*ca.* +0.11) signals are subject to relatively large upfield shifts in the presence of **3**, whereas other



II

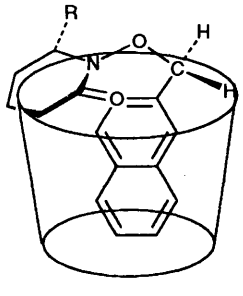
outside-proton signals ($\Delta\delta$ = 0 to +0.02) are not. This finding supports the view that a more hydrophobic naphthyl group, being generally assumed to fit better,[1,6,13] is preferentially immersed into the β-CDx cavity from the secondary hydroxy-group side of this CDx. Surprisingly, the presence of β-CDx causes a large upfield shift of the H^5 ($\Delta\delta$ = +0.13) and (particularly) H^6 (+0.40) signals of the guest **3**, whereas the β-CDx complexation with **3** exerts negligible effects on other proton ($\Delta\delta$ = −0.02 for the H^3 and +0.02 for H^4) and methylene proton (−0.01) signals. Since both the pyridone and naphthalene chromophores of **3** cannot penetrate deeply into the cavity, this dramatic upfield shift of the H^6 signal forces us to propose the complex structure **III** in which a major part of the



III

planar pyridone ring sticks out from the cavity but leaving the H^6 proton above the naphthalene ring axially incorporated into the cavity. The structure **III** also provides a good explanation for the ICD spectral behaviour of **3** observed in the presence of β-CDx.

An analysis of the ICD spectrum of the **5**–β-CDx complex establishes the preferential axial inclusion of a 2-naphthyl group into the cavity as well as the perpendicular orientation (to the cavity axis) of the C^3–C^6 axis in the pyridone ring. The problem is whether the pyridone-ring protons H^3–H^6 are situated in the shielding or the deshielding region of the naphthalene ring in **5**. β-CDx induces distinct downfield shifts of the pyridone-ring proton signals ($\Delta\delta$ = −0.04, −0.04 and −0.06 for H^3, H^5 and H^6, respectively) in addition to the methylene proton signal (−0.07), being in sharp contrast to the case of the **3**–β-CDx complex. Since the pyridone-ring protons must be located within the deshielding zone of the naphthalene ring, we can visualize the complex structure **IV** in which the



IV

pyridone moiety is placed at the rim of the β-CDx cavity so as to cover this cavity. The structure **IV** can also explain a downfield shift of signal for the methylene protons which are situated in the deshielding zone of the amide carbonyl group. The very small effects of a methyl substituent on the structure and stability of the **3**–β-CDx and **5**–β-CDx complexes provide a strong piece of evidence in support of the pyridone chromophore that is located around the rim of the secondary hydroxy-group side of the β-CDx cavity as depicted in the proposed complex structures **III** and **IV**.

Recently Kodaka has predicted on the basis of the coupled oscillator theory that the ICD sign for a guest included outside the β-CDx cavity becomes opposite to that located inside the cavity.[14] This reversal of the ICD sign is extremely prominent on the narrower rim side of β-CDx but it does not occur significantly on the wider rim side. The negligible shift of the 6-H signal of β-CDx in the presence of the guest **3** or **5** strongly suggests that the intracavity inclusion of these guests takes place from the secondary hydroxy-group side as already mentioned. Thus, the Kuroda rule is considered to be not applicable to our host–guest systems.

The presence of 20% (v/v) CD_3OD, added to solubilize **5** with much less solubility than **3**, causes further upfield shifts of the 3-H ($\Delta\delta$ = +0.04) and 5-H (*ca.* +0.05) signals of β-CDx, relative to those in 4% (v/v) CD_3OD–D_2O. These proton signals are likely to shift as a result of proximal or direct interactions with CD_3OD. These interactions may be responsible for the smaller upfield shifts of the 3-H ($\Delta\delta$ = +0.04) and 5-H (+0.07) signals observed in the presence of 20% (v/v) CD_3OD, suggesting the formation of a ternary inclusion complex the structure of which has attracted much attention owing to its complicated nature.[15] The finding that a similar ICD spectrum is obtained in either 4% (v/v) MeOH–H_2O or 20% (v/v) MeOH–H_2O demonstrates that the increased concentration of CD_3OD does affect the guest conformation within the cavity to, if any, only a small extent. β-CDx has been demonstrated to associate with MeOH in aqueous solution giving a 1:1 inclusion complex[16] and, hence, our β-CDx inclusion complexes with **1**–**6** formed in the presence of MeOH may be taken as the guest–MeOH–β-CDx ternary complexes. If a ternary complex with a 1:1:1 stoichiometry exists, the obtained equilibrium constant K becomes equal to $K'[MeOH]_0$. The MeOH concentration was kept constant throughout this study so that we find that it is reasonable to discuss the extent of β-CDx complexation in terms of the K values. Further characterization of such a ternary complex is beyond the scope of our present study; we must await future studies to discuss this subject in detail.

Experimental

Materials and Solvents.—1-Benzyloxy-2-pyridone (**1**), 1-benzyloxy-6-methyl-2-pyridone (**2**), 1-(1-naphthyl)methyloxy-2-pyridone (**3**), 1-(1-naphthyl)methyloxy-6-methyl-2-pyridone (**4**), 1-(2-naphthyl)methyloxy-2-pyridone (**5**), 1-(2-naphthyl)-methyloxy-6-methyl-2-pyridone (**6**) and 1-ethoxy-2-pyridone were prepared according to the previously described procedures.[5b,17,18] The crude products obtained (**1**–**6**) were purified by column chromatography over silica gel (70–230 mesh, Merck) using $CHCl_3$ as the eluent followed by repeated recrystallization from hexane–EtOAc to give analytically pure samples. 1-Ethoxy-2-pyridone was purified by distillation at reduced pressure. The physical properties of **1**, **2** and 1-ethoxy-2-pyridone were compatible with those of the previously prepared compounds. The physical properties of other materials are as follows. **3**, M.p. 62–63 °C (from hexane–EtOAc); ν_{max} 1665 cm^{-1} (CO) (Found: C, 76.5; H, 5.3; N, 5.6. $C_{16}H_{13}NO_2$ requires C, 76.48; H, 5.21; N, 5.57%). **4**, M.p.

132–133 °C (from EtOAc–hexane); ν_{max} 1660 cm^{-1} (CO) (Found: C, 77.1; H, 5.8; N, 5.3. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%). **5**, M.p. 130–132 °C (from EtOAc–hexane); ν_{max} 1660 cm^{-1} (CO) (Found: C, 76.4; H, 5.3; N, 5.6%). **6**, M.p. 101–103 °C (from EtOAc–hexane); ν_{max} 1670 cm^{-1} (CO) (Found: C, 77.2; H, 5.9; N, 5.3%). The structures of **3–6** were also established by measuring ^1H NMR spectra of these new materials in $CDCl_3$ containing tetramethylsilane as an internal standard. 1-Naphthalene- and 2-naphthalene-methanols (Aldrich) were employed as received. The α- and β-cyclodextrins from Aldrich or Fluka were used without further purification.

Distilled water was purified by passage through a Millipore Milli-Q system. Methanol (Aldrich) was of spectroscopic grade and was used as supplied along with deuterium oxide (99.9 atom%, Aldrich) and [$^2H_4$] methanol (99.8 atom%, Aldrich).

Measurements.—UV absorption and ICD spectra were recorded on a Shimadzu UV-2200 spectrophotometer and a JASCO J-600 spectrodichrometer at 24 ± 1 °C, respectively. A cell with a 10 mm pathlength was employed. 200 MHz ^1H NMR spectra in D_2O containing 4% (v/v) CD_3OD or 20% (v/v) CD_3OD were measured with a JEOL FX-200 spectrometer at 24 ± 1 °C. Chemical shifts were determined by using sodium [2,2,3,3-$^2H_4$]3-trimethylsilylpropionate (Merck) as an external standard.

Although the 5-H and 6-H signals of β-CDx strongly overlap giving an unresolved broad peak in D_2O, the addition of small amounts of CD_3OD (4 vol%) causes a slight upfield shift of not the 6-H, but the 5-H signal ($\Delta\delta = +0.01$). This shift enabled us to determine fairly accurately the chemical shift of the 5-H proton. Assignments of the β-CDx-proton signals were made in the same manner as that described in the literature.[19] The pyridone ring-proton signals were previously assigned on the basis of NOE experiments in $CDCl_3$.[5b] The coupling pattern and constants obtained for each proton made it possible to make unambiguous assignments of the ring-proton signals in D_2O.

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