Inclusion complexation of (cyclo)alkanes and (cyclo)alkanols with 6-*O*-modified cyclodextrins

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Novel α- and/or β-cyclodextrin benzoates (2α, 2β), methyl phthalate (3β), tethered benzamide (4β) and 2-naphthoate (5β) have been synthesized. The complex stability constants (K_s) of these cyclodextrin derivatives with a series of acyclic and cyclic hydrocarbons, and alcohols have been determined in water to reveal the role of the hydrophilic group in the guest molecule, and to evaluate the individual contribution of weak interactions involved in inclusion complexation by cyclodextrin. The free energy of complexation ($-\Delta G^\circ$) increases linearly to a certain limit with extending chain length or ring size (N_C) of the guests, giving unit increments per methylene ($-d\Delta G^\circ/dN_C$). Interestingly, the unit increment obtained is independent of the host's size or substituent introduced, but is a critical function of the guest type. Thus, a remarkably large $-d\Delta G^\circ/dN_C$ value of 5.4 kJ mol^{-1} has been obtained for the cycloalkane series, whereas much smaller, but conventional, values have been recorded for cycloalkanols (3.3 kJ mol^{-1}), alkanes (3.1 kJ mol^{-1}) and alkanols (2.7 kJ mol^{-1}). No significant isotope effects on K_s are observed when deuterated cyclohexane is complexed with the same cyclodextrins. Similarly, there is no significant effect when deuterated water is used as solvent. Moderate enantioselectivities of up to 2.0 are obtained with some chiral guests.

Introduction

A variety of cyclodextrin derivatives have hitherto been synthesized in order to modify or enhance the original molecular recognition properties of the native cyclodextrins. These modified cyclodextrins have widely been employed, for example, as enzyme mimics, supramolecular receptors and chiral selectors in separation science and technology.[1–8] The molecular recognition behavior of native and modified cyclodextrins is governed by several cooperative weak forces, including van der Waals, hydrophobic, electrostatic, dipole–dipole and hydrogen-bonding interactions.[1,2,7,8] Hence, it is not always possible to specify the major contributor(s) to the host–guest complexation, even in the case of a relatively simple molecular host like cyclodextrin. To eliminate possible contributions from electrostatic, dipole–dipole and hydrogen-bonding interactions, we employed a series of cycloalkanes and cycloalkenes as guests in a molecular recognition study which used β-cyclodextrin 6-*O*-monobenzoate as the host.[9] In a previous study we demonstrated that, in the absence of extra weak interactions which serve to complicate matters, the complexation behavior of cyclodextrin with hydrocarbon guests can be more explicitly understood in terms of the size, conformation, configuration, substituent type and rigidity of the guest molecule.[9]

We now wish to report our study on the synthesis and inclusion complexation of some novel 6-*O*-modified α- and β-cyclodextrins (**2**α, **2**β–**5**β) with varying cavity size, substituent and tether group. The complexation behavior of these modified cyclodextrins with a series of (cyclo)alkanes and (cyclo)alkanols was comparatively studied in aqueous solutions by differential circular dichroism spectroscopy. The results reveal the effects of the guest's size and hydrophobicity and of the host's substituent type, cavity size and hydrophobicity. The deuterium isotope effects upon complexation of both guest and solvent, and the enantiodifferentiation of chiral guests by these modified cyclodextrins are also discussed.

Experimental

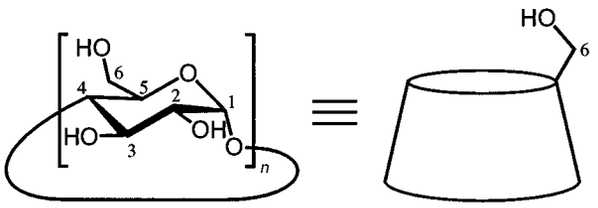
General

Melting points were measured with a YANACO MP-21 apparatus and are uncorrected. Mass spectra were obtained on a JEOL JMS-DX-303 instrument. ^{1}H and ^{13}C NMR spectra were recorded in [$^2H_6$]dimethyl sulfoxide ([$^2H_6$]DMSO) or in 1:1 [$^2H_4$]methanol–[$^2H_2$]water (CD_3OD–D_2O) on a JEOL GX-400 or a Bruker AMX600 spectrometer. IR and UV spectra were obtained on a Nicolet 10DX, a JASCO A100 or an IR-810 instrument and on a Shimadzu UV-240 or JASCO Ubest-50 spectrophotometer, respectively. Circular dichroism spectra were measured in a cylindrical quartz cell (light path 1 cm; volume 2.7 cm^3) or a conventional quartz cell (light path 1 cm) on a JASCO J-720 or a J-720W spectropolarimeter equipped with a PTC-348WI temperature controller.

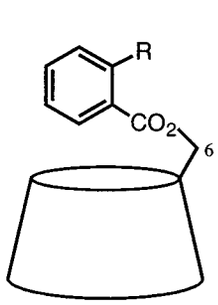
Materials

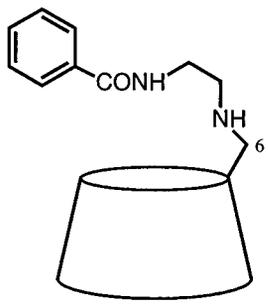
Most (cyclo)alkanes and (cyclo)alkanols employed as guests were commercially available and were used as received, except for cyclononanol, which was prepared by the reduction of cyclononanone with $LiAlH_4$. Deionized and distilled water and distilled methanol were used as solvents. α- and β-Cyclodextrins (Kanto Chemical Co.) were dried *in vacuo* at 80 °C for 5 h prior to use.

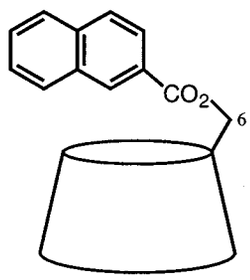
α- and β-Cyclodextrin 6-*O*-benzenecarboxylates (**2**α and **3**β) were synthesized in the reactions of α- and β-cyclodextrins with the corresponding aroyl chlorides, according to similar pro-



1α $n = 6$
1β $n = 7$







2α R = H
2β R = H
3β R = CO_2Me

4β

5β

cedures described previously for **2**β and **5**β.[9,10] 6-[(*N*-Benzoyl-2-aminoethyl)amino]-6-deoxy-β-cyclodextrin (**4**β) was prepared from 6-[(2-aminoethyl)amino]-6-deoxy-β-cyclodextrin according to the reported procedures.[10]

Typical synthetic procedures are described for **2**α. Benzoyl chloride (0.48 cm^3, 4.11 mmol) in dry pyridine (50 cm^3) was added dropwise over 10 min to a solution (1.6 dm^3) of α-cyclodextrin (8.0 g, 8.22 mmol) in dry pyridine at −7 °C. The resultant solution was stirred for an additional 5.5 h at room temperature and then quenched by the addition of water (1 cm^3). Pyridine was distilled under reduced pressure at 40–50 °C to leave a solid white residue, which was extracted for 30 h with acetone, using a Soxhlet apparatus. The remaining solid was recrystallized from water to give pure **2**α (0.955 g), which afforded a single spot at R_f 0.37 upon TLC analysis over silica gel with an acetonitrile–water (4:1) eluent. Yield 14%; mp 277–279 °C (dec.); *m*/*z* [FAB(NaI)] 1100 ($M + Na^+$), 1078 ($M + H^+$); $\lambda_{max}(H_2O)$/nm (ε/mol^{-1} dm^3 cm^{-1}) 232.6 (10 600), 274.9 (920), 283.0 (800); ν(KBr)/cm^{-1} 3432, 1719, 1639, 1454, 1286, 1155, 1078, 1028, 951, 752; $\delta_H([^2H_6]DMSO)$ 8.00 (d, 2H, *ortho*), 7.67 (t, 1H, *para*), 7.54 (t, 2H, *meta*), 5.48–5.63 [m, 12H, (O-2)H and (O-3)H], 4.80–4.86 (br d, 6H, H-1), 4.45–4.64 [m, 5H, (O-6)H], 4.05 (br s, 1H, H-5′), 3.29–3.84 (m, H-3, H-5, H-6, H-2, H-4 and water); $\delta_C([^2H_6]DMSO)$ 165.66 (C=O), 133.55 (*ipso*), 129.60 (*p*), 129.36 (*o*), 128.91 (*m*), 102.49, 102.12, 102.02, 101.79 (C-1′, C-1), 82.58, 82.18, 82.00, 81.87 (C-4′, C-4), 73.27 (C-3), 72.15 (C-2, C-5), 68.96 (C-5′), 64.24 (C-6′), 59.98, 59.88 (C-6) (Found: C, 45.49; H, 6.01. Calc. for $C_{43}H_{64}O_{31}\cdot 3H_2O$: C, 45.66; H, 6.24%). **3**β: Yield 7.7%; mp 336–337 °C (dec.); *m*/*z* [FAB(NaI)] 1319 ($M + Na^+$); λ_{max}(MeOH)/nm (ε/mol^{-1} dm^3 cm^{-1}) 225.0 (8200), 277.0 (1260); $\lambda_{max}(H_2O)$/nm (ε) 228.0 (7160), 276.0 (1500); ν(KBr)/cm^{-1} 3320 (s), 2900 (m), 1720 (m), 1630 (w), 1290 (m), 1150 (s), 1080 (s), 1020 (s), 940 (m), 860 (w), 750 (w), 700 (w), 580 (w); $\delta_H([^2H_6]DMSO)$ 7.9 (d, 1H), 7.6 (m, 3H), 5.5–5.9 (m, 14H), 4.7–4.9 (m, 7H), 4.2–4.6 (m, 6H), 3.9 (br, 1H), 3.7 (s, 3H), 3.2–3.7 (m, 40H); $\delta_C(CD_3OD–D_2O)$ 170.63, 169.40, 133.57, 133.18, 133.11, 132.09, 130.32, 129.82, 104.02, 103.79, 103.70, 103.53, 102.90, 83.55, 82.75, 82.54, 82.41, 82.29, 82.07, 75.29, 74.79, 74.68, 74.50, 73.73, 73.51, 73.36, 73.21, 73.14, 71.64, 66.84, 61.59, 61.41, 61.28, 61.12, 60.86, 53.97 (Found: C, 44.70; H, 5.75. Calc. for $C_{51}H_{76}O_{38}\cdot 4H_2O$: C, 44.74; H, 6.18%).

Spectrometric measurements

Complexation by the modified cyclodextrins was best detected by circular dichroism (CD) spectrometry, while the UV spectra did not show any significant changes even upon addition of a large excess of the guest. The CD spectra of cyclodextrins **2**–**5**, at a concentration of 25–50 μmol dm^{-3}, were measured at 25 °C in the presence of varying concentrations of the guest in water. The differential CD spectra were obtained by subtracting the original CD spectrum, recorded in the absence of a guest, from those recorded in the presence of a guest.

Results and discussion

Circular dichroism spectra

The absorption and circular dichroism spectra of α-cyclodextrin 6-*O*-monobenzoate (**2**α), β-cyclodextrin 6-*O*-monobenzoate (**2**β), methyl phthalate (**3**β) and 2-naphthoate (**5**β), and 6-[(*N*-benzoyl-2-aminoethyl)amino]-6-deoxy-β-cyclodextrin (**4**β) are shown in Figs. 1 and 2. The CD extrema (λ_{ext}) and intensity ($\Delta\varepsilon_{ext}$) determined in water, mixed water–methanol and methanol solutions are listed in Table 1.

As can be seen from Fig. 1 and Table 1, α- and β-cyclodextrin 6-*O*-monobenzoates (**2**α, **2**β) afford quite similar CD profiles, exhibiting a relatively large negative Cotton effect for the ^1L_a band around 235 nm and a small negative Cotton effect for the ^1L_b band around 275 nm, irrespective of the solvent composition employed. On the basis of the 'sector rule' proposed by Kajtar *et al.*,[11] we deduce that the benzoate moieties of **2**α and **2**β are not deeply included in the cavity but are only perching on the rim of the primary side of cyclodextrin, as depicted schematically in Fig. 3(*a*). This conformation, in which both the ^1L_a and ^1L_b transition moments lie in the negative region, appears reasonable, since the benzoate group is directly connected to one of the primary hydroxy groups and the ester linkage is not long enough to allow deep penetration of the phenyl group into the cavity. Similar conformations are anticipated for the phthalate derivative **3**β, based on the negative Cotton effect peaks observed for the ^1L_a and ^1L_b bands.

Conversely, the benzoyl group in **4**β, which is connected with a long ethylenediamine chain, can be well accommodated in the cavity of cyclodextrin. Hence, **4**β shows a large positive Cotton

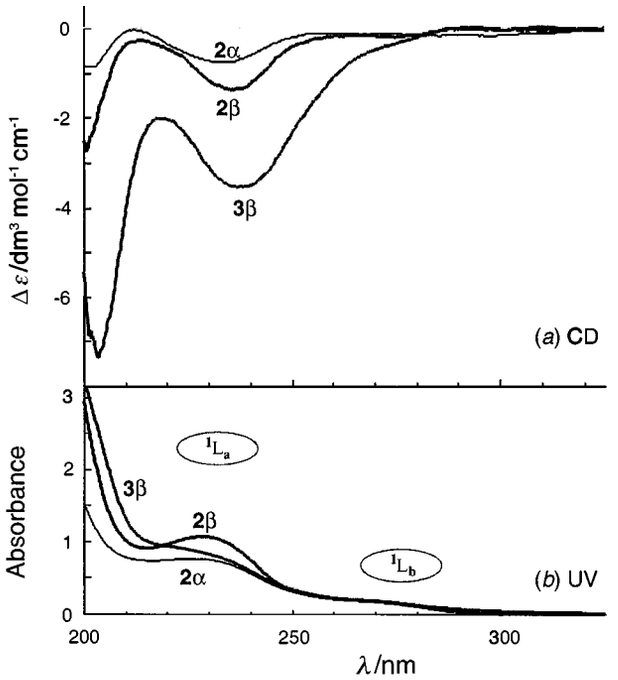


Fig. 1 (*a*) Circular dichroism and (*b*) absorption spectra of α-cyclodextrin 6-*O*-monobenzoate (**2**α) in water (50 μmol dm^{-3}), and of β-cyclodextrin 6-*O*-monobenzoate (**2**β) and methyl phthalate (**3**β) in 1:1 CH_3OH–H_2O (50 μmol dm^{-3}). The absorbance values are calculated from the high voltage applied to the photomultiplier tube of the CD spectrometer and are not calibrated.

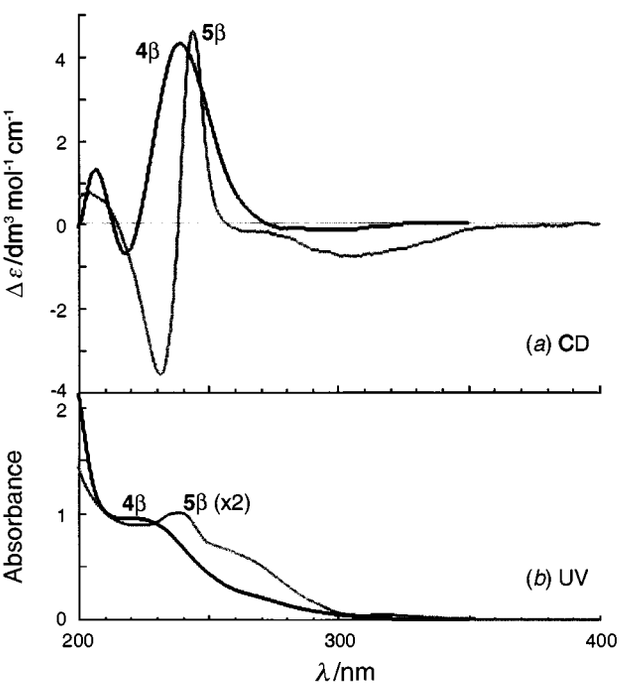


Fig. 2 (*a*) Circular dichroism and (*b*) absorption spectra of 6-[(*N*-benzoyl-2-aminoethyl)amino]-6-deoxy-β-cyclodextrin (**4**β, 50 μmol dm^{-3}) and β-cyclodextrin 6-*O*-mono-2-naphthoate (**5**β, 25 μmol dm^{-3}) in H_2O. The absorbance is determined as in Fig. 1.

effect for the ^1L_a band at 239 nm and a small negative Cotton effect for the ^1L_b band at 279 nm (Fig. 2) in accordance with the sector rule illustrated in Fig. 3(*b*). Although no empirical rule is known to elucidate the conformation of a naphthalene-modified cyclodextrin, examinations with Corey–Pauling–Koltun (CPK) molecular models show that the naphthyl group in **5**β cannot penetrate into the cavity, but instead lies just above the rim. This structural speculation may be justified in part by the X-ray structure of an inclusion complex of 2-naphthoic

Table 1 Circular dichroism extrema (λ_{ext}) and intensity ($\Delta\varepsilon_{ext}$) of modified cyclodextrins **2**–**5** in methanol–water[a]

	λ_{ext}/nm ($\Delta\varepsilon_{ext}$/dm^3 mol^{-1} cm^{-1})		
Host	H_2O	50% MeOH	MeOH
2α	234 (−0.72)	236 (−1.38)	234 (−1.34)
	277 (−0.14)	274 (−0.17)	274 (−0.18)
		282 (−0.16)	284 (−0.18)
2β	234 (−1.05)	236 (−1.11)	234 (−0.98)
	274 (−0.20)	274 (−0.10)	273 (−0.05)
	282 (−0.10)	284 (−0.08)	283 (−0.06)
3β[b]	204 (−9.27)	238 (−3.55)	234 (−1.59)
	238 (−5.47)		
4β	207 (+1.31)		
	218 (−0.69)		
	239 (+4.31)		
	279 (−0.11)		
5β	205 (+0.75)		
	231 (−3.59)		
	244 (+4.60)		
	307 (−0.75)		

[a] [Host] = 5×10^{-5} mol dm^{-3}. [b] The λ_{ext} ($\Delta\varepsilon_{ext}$) values are 238 (−4.51) and 237 (−2.75) in 25 and 75% methanol solutions, respectively.

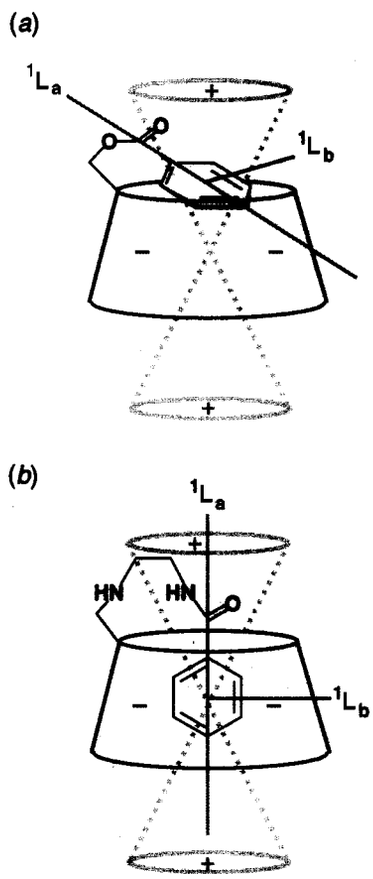


Fig. 3 Sector rule applied to self-inclusion of aromatic moiety of (*a*) **2**α, **2**β and (*b*) **4**β

acid with heptakis(2,6-di-*O*-methyl)-β-cyclodextrin, in which the naphthalene moiety is shallowly inserted lengthwise into the host cavity from the primary side at an angle of *ca.* 30°.[12]

Complexation equilibrium

As has been demonstrated in a previous paper,[9] the addition of a guest into aqueous solutions of cyclodextrin derivatives causes significant changes to the CD spectra, but no appreciable deviations are observed in the absorption spectra. Representative changes in CD and differential CD spectra are shown in Fig. 4 for the complexation of nonan-1-ol with α-cyclodextrin

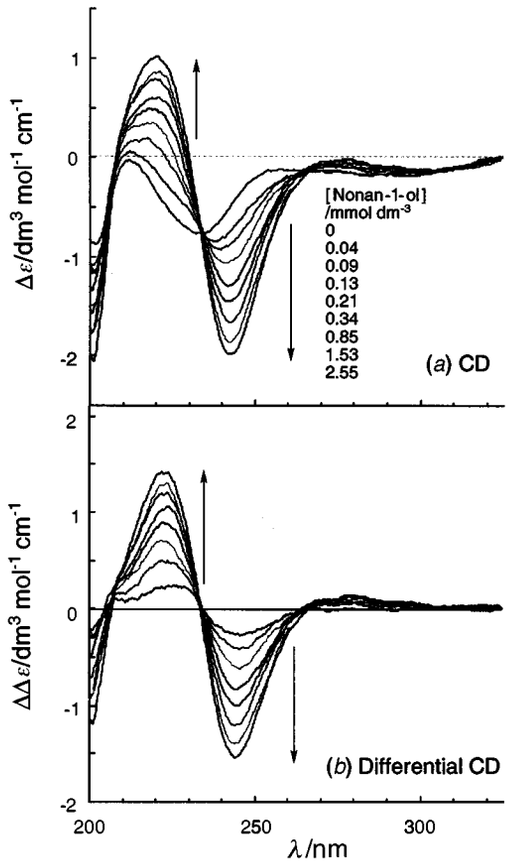


Fig. 4 (*a*) CD and (*b*) differential CD spectral changes of aqueous solutions of **2**α (50 μmol dm^{-3}) in the presence of nonan-1-ol, added as a guest

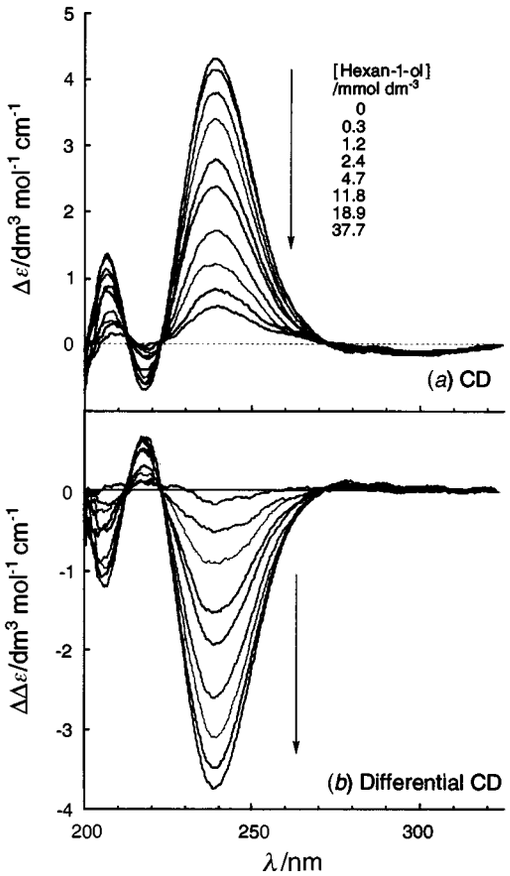


Fig. 5 (*a*) CD and (*b*) differential CD spectral changes of aqueous solutions of **4**β (50 μmol dm^{-3}) in the presence of hexan-1-ol, added as a guest

benzoate **2**α. The CD spectrum of β-cyclodextrin benzoate **2**β shows similar behavior upon addition of guests. In contrast, the CD intensities of phthalate **3**β, benzamide **4**β and naphthoate **5**β are reduced dramatically by adding guests, as exemplified in Fig. 5, which shows the complexation of hexan-1-ol with **4**β. The opposite CD spectral changes observed for these two categories of hosts should reflect the differences in both conformational and positional changes of the appended chromophores upon the addition of guest.

The 1 : 1 inclusion complexation of a guest (G) with modified cyclodextrin (H) is expressed by eqn. (1). The CD spectral

$$H + G \overset{K_s}{\rightleftharpoons} H{\cdot}G \quad (1)$$

change ($\Delta\Delta\varepsilon$) upon addition of guest, defined as $\Delta\Delta\varepsilon = \Delta\varepsilon$ (with guest) − $\Delta\varepsilon$ (without guest), is assumed to be proportional to the concentration of inclusion complex produced, *i.e.* $\Delta\Delta\varepsilon = a[H{\cdot}G]$. The proportionality coefficient a is taken as a sensitivity factor for the CD change induced by the addition of one molar guest, or a quantitative measure of the conformational changes upon complexation.[9] Then, the complex stability constant (K_s) is given by eqn. (2), where $[H]_0$ and $[G]_0$ are the initial concentrations of host and guest.

$$K_s = \frac{[H{\cdot}G]}{[H][G]} = \frac{\Delta\Delta\varepsilon/a}{([H]_0 - \Delta\Delta\varepsilon/a)([G]_0 - \Delta\Delta\varepsilon/a)} \quad (2)$$

When the concentration of the complex formed is much smaller than the initial guest concentration, *i.e.* $[G]_0 \gg [H{\cdot}G]$ and therefore $[G] \cong [G]_0$, the K_s value is calculated from the reciprocal slope of eqn. (3). According to this approximation,

$$\Delta\Delta\varepsilon = -(1/K_s)(\Delta\Delta\varepsilon/[G]_0) + a[H]_0 \quad (3)$$

the $\Delta\Delta\varepsilon$ value was plotted against the $\Delta\Delta\varepsilon/[G]_0$ value, allowing a good straight line in our previous study,[9] where the K_s values are relatively low (<2000 mol^{-1} dm^3). However, in the present case, where water is used as a solvent, the K_s value often exceeds this limit and the $\Delta\Delta\varepsilon/[G]_0 - \Delta\Delta\varepsilon$ plot deviates significantly from the regression line. Representative plots are shown in Fig. 6(*a*) for complexation of cyclohexanol, heptane and cycloheptane with **2**β.

Although the plot for cyclohexanol gives a good linear fit in Fig. 6(*a*) and a reasonable K_s value is obtained, the corresponding plots for heptane and cycloheptane show a departure from the regression lines. Hence, in the present work, eqn. (2) is solved for $\Delta\Delta\varepsilon$ to give eqn. (4) and the curve fitting, using a

$$\Delta\Delta\varepsilon = \{a([H]_0 + [G]_0 + 1/K_s) \pm \sqrt{a^2([H]_0 + [G]_0 + 1/K_s)^2 - 4a^2[H]_0[G]_0}\}/2 \quad (4)$$

non-linear least squares method, was employed in the determination of K_s values. As shown in Fig. 6(*b*), no serious deviations are found in the curve fitting, which in turn confirms the 1 : 1 stoichiometry for the host–guest complexation by the modified cyclodextrins. When repeated measurements were made, the K_s value was reproducible within an error of ±5%, which corresponds to an estimated error of 0.15 kJ mol^{-1} in the free energy of complexation ($\Delta G°$).

By using this method, we can estimate the ultimate CD changes ($\Delta\Delta\varepsilon_{max}$) at a guest concentration of 10 mol dm^{-3} by extrapolation of the curve fitting to much higher concentrations which lie beyond the experimental region. The $\Delta\Delta\varepsilon_{max}$ value thus obtained is a good measure of guest penetration into the cavity, since deeper penetration inevitably causes larger CD changes as far as the same host is concerned. The sensitivity factor (a), ultimate CD changes ($\Delta\Delta\varepsilon_{max}$), stability constant

(K_s), and free energy change ($-\Delta G°$) for all host–guest combinations examined are listed in Table 2.

Molecular recognition

We will first discuss the complexation behavior of each of the modified cyclodextrins with (cyclo)alkanes and (cyclo)alkanols. The complex stability constant (K_s) generally increases with an increasing number of methylene units (N_C) in the guest molecule, but the effects of N_C upon K_s depend critically on the host's cavity size and the substituent introduced, as well as the guest structure.

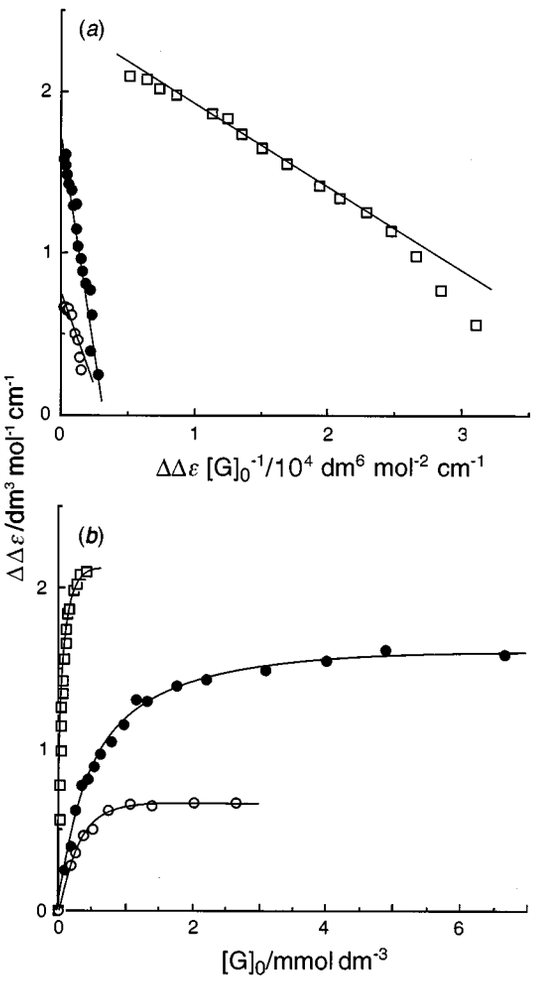


Fig. 6 (*a*) Linear and (*b*) curve fitting analyses, according to eqns. (3) and (4), for complexations of cyclohexanol (●), heptane (○) and cycloheptane (□) with **2**β in H_2O

α- and β-Cyclodextrin benzoates (2α, 2β). Possessing different cavity sizes, the cyclodextrin benzoates **2**α and **2**β showed contrasting complexation behavior towards (cyclo)alkanes and (cyclo)alkanols, which is distinctly different from that of the native cyclodextrins (**1**α and **1**β). As can be seen from Fig. 7(*a*), the addition of a benzoate group to **1**α, affording **2**α, does not enhance but rather reduces the binding affinity for alkan-1-ols, particularly for longer ones ($N_C \geqslant 6$). This leads to substantially smaller K_s values for cycloalkanols than those reported for **1**α.[13] It is likely that the benzoate moiety introduced interferes, or competes, with the penetration of the over-sized guest molecules into the narrow cavity of α-cyclodextrin. α-Cyclodextrin benzoate **2**α binds alkanes more strongly than alcohols of corresponding chain length. This indicates that the alcohol's hydroxy group does not contribute to the complex stability through hydrogen bonding interactions, but diminishes K_s by its increased hydrophilicity.

In contrast, the introduction of a benzoate residue to β-cyclodextrin significantly strengthens the binding ability of modified cyclodextrin **2**β. As shown in Fig. 7(*b*), the K_s values for complexation of **2**β with alkanols and cycloalkanols are increased by more than half an order of magnitude as compared to those for native **1**β. Since the inner diameter of the β-cyclodextrin cavity[14] is formally large enough to accommodate these guest molecules, and the tethered benzoate group is only perching on the rim, the enhanced K_s values are attributed to the higher hydrophobicity, or expanded cavity of **2**β. Another interesting feature of the complexation behavior of **2**β is the apparent saturation of K_s at larger N_C. In contrast to the linear increase of log K_s for acyclic guests of up to $N_C = 11$, the log K_s value for cycloalkanols levels out at $N_C = 7$ for **1**β and at $N_C = 8$ for **2**β. The delayed saturation observed for **2**β may be attributed to the expanded cavity caused by the modification. In this context, it is somewhat surprising that the K_s values for adamantan-1- and -2-ols, plotted at $N_C = 10$ in Fig. 7(*b*) (1- and 2-Ad), almost fall on the extended regression line for simple cycloalkanols.

Acyclic and cyclic hydrocarbons are accommodated better in **2**β than the corresponding alcohols by a factor of 2–10, as judged from the K_s value. Furthermore, these hydrocarbons, which lack hydrophilic functional groups, afford appreciably larger slopes in the N_C − log K_s plot, probably owing to the larger hydrophobic effect in the aqueous phase, as well as the stronger van der Waals interactions in the cavity.

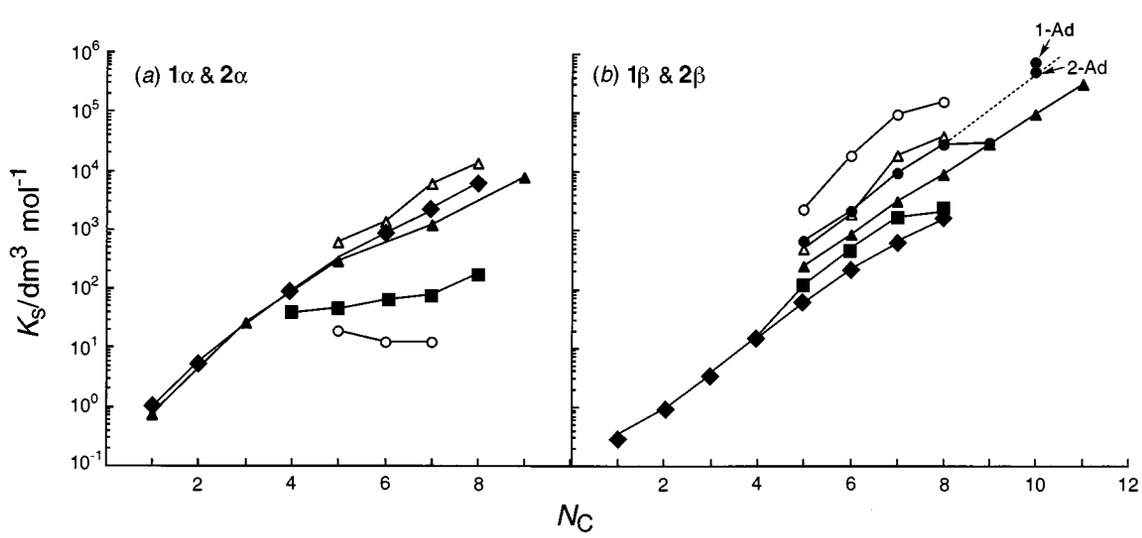


Fig. 7 Complex stability constant (K_s) plotted as a function of the number of methylenes (N_C) in the guest molecule for the complexation of a series of alkanes (△), alkan-1-ols (▲), cycloalkanes (○) and/or cycloalkanols (●) with (*a*) **2**α and (*b*) **2**β in H_2O. The corresponding data for complexation of alkanols (◆) and cycloalkanols (■) with native cyclodextrins (**1**α and **1**β) are also plotted.

Table 2 Sensitivity factor (a),[a] ultimate CD change ($\Delta\Delta\varepsilon_{max}$),[b] complex stability constant (K_s) and free energy change ($-\Delta G^\circ$) for inclusion complexation of modified cyclodextrins with a series of (cyclo)alkanes and (cyclo)alkanols in H_2O and in D_2O at 25 °C[c]

Host	Guest	a[a]	$\Delta\Delta\varepsilon_{max}$[b]/dm^3 mol^{-1} cm^{-1}	K_s/dm^3 mol^{-1}	$-\Delta G^\circ$/kJ mol^{-1}
2α	Pentane	22 200	1.11	607	15.9
	Hexane	10 200	0.51	1 370	17.9
	Heptane	8 200	0.41	5 830	21.5
	Octane	5 300	0.27	12 900	23.4
	Methanol	9 200	0.41	0.71	−0.8
	Propan-1-ol	21 200	1.05	25	8.0
	Pentan-1-ol	32 000	1.59	285	14.0
	Heptan-1-ol	30 900	1.55	1 210	17.6
	Nonan-1-ol	28 300	1.42	7 380	22.1
	Cyclopentanol	25 500	1.20	24	7.9
	Cyclohexanol	33 300	1.65	12	6.2
	Cycloheptanol	34 700	1.73	12	6.2
	1,4-Dioxane	8 140	0.40	5.1	4.0
2β	Pentane	24 500	1.22	478	15.3
	Hexane	31 100	1.55	1 870	18.7
	Heptane	13 600	0.68	18 500	24.3
	Octane	8 860	0.44	38 700	26.2
	Pentan-1-ol	33 400	1.71	242	13.6
	Hexan-1-ol	33 200	1.70	868	16.8
	Heptan-1-ol	34 800	1.78	3 040	19.9
	Octan-1-ol	35 600	1.81	8 890	22.5
	Nonan-1-ol	35 300	1.80	30 000	25.5
	Decan-1-ol	35 300	1.80	94 100	28.4
	Undecan-1-ol	29 900[d]	1.49	312 000	31.3
	Cyclopentane	33 500	1.68	2 360	19.2
	Cyclopentane[e]	58 700[f]	1.96	3 090	19.9
	Cyclohexane	35 200	1.76	19 000	24.4
	Cyclohexane[e]	44 000[f]	2.21	18 500	24.3
	[$^2H_{12}$]Cyclohexane	33 500	1.66	20 200	24.6
	Cycloheptane	36 700	1.84	97 700	28.5
	Cycloheptane[e]	45 300[f]	2.27	78 300	27.9
	Cyclooctane	35 800	1.78	154 000	29.6
	Cyclooctane[e]	45 000[f]	2.25	240 000	30.7
	Cyclopentanol	32 700	1.67	647	16.0
	Cyclopentanol[e]	32 400[f]	1.62	726	16.3
	Cyclohexanol	34 800	1.79	2 100	19.0
	Cyclohexanol[e]	36 700[f]	1.88	3 390	20.1
	Cycloheptanol	39 900	2.04	9 500	22.7
	Cycloheptanol[e]	41 500[f]	2.08	11 300	23.1
	Cyclooctanol	42 700	2.18	30 100	25.5
	Cyclooctanol[e]	40 700[f]	2.04	34 000	25.9
	Cyclononanol	30 900	1.55	30 500	25.6
	Adamantan-1-ol	51 600	2.63	506 000	32.5
	Adamantan-2-ol	51 500	2.58	737 000	33.5
	1,4-Dioxane	24 800	1.24	62	10.2
3β	Pentan-1-ol	71 600	3.59	52	9.8
	Heptan-1-ol	77 100	3.85	315	14.3
	Nonan-1-ol	64 600	3.23	1 670	18.4
	Cyclopentane	72 900	3.65	316	14.3
	Cyclohexane	79 000	3.95	2 690	19.6
	Cycloheptane	90 000	3.96	10 900	23.0
	Cyclooctane	71 800	3.60	41 200	26.3
	Cyclopentanol	88 400	4.39	98	11.4
	Cyclohexanol	86 800	4.33	381	14.7
	Cycloheptanol	84 000	4.21	1 480	18.1
	Cyclooctanol	84 400	4.23	2 930	19.8
	Cyclononanol	93 800	4.69	4 060	20.6
4β	Pentan-1-ol	97 400	4.63	33	8.7
	Hexan-1-ol	96 800	4.70	103	11.5
	Heptan-1-ol	92 900	4.54	317	14.3
	Octan-1-ol	83 700	4.10	782	16.5
	Nonan-1-ol	83 300	4.08	1 230	17.6
	Cyclopentane	63 200	3.08	198	13.1
	Cyclohexane	83 300	4.08	1 730	18.5
	Cycloheptane	99 810	4.89	5 370	21.3
	Cyclooctane	93 100	4.56	10 100	22.8
	Cyclopentanol	107 000	5.19	71	10.6
	Cyclohexanol	110 000	5.35	240	13.6
	Cycloheptanol	110 000	5.38	875	16.8
	Cyclooctanol	106 000	5.22	2 110	19.0
	Cyclononanol	124 000[d]	6.21	2 310	19.2
5β	Pentane	140 000[d]	7.00	2 620	19.5
	Hexane	155 000[d]	7.74	8 300	22.4
	Pentan-1-ol	163 000[d]	8.21	361	14.6
	Octan-1-ol	150 000[d]	7.59	8 900	22.5
	Decan-1-ol	143 000[d]	7.13	84 300	28.1

Table 2 (*Contd.*)

Host	Guest	a[a]	$\Delta\Delta\varepsilon_{max}$[b]/dm^3 mol^{-1} cm^{-1}	K_s/dm^3 mol^{-1}	$-\Delta G°$/kJ mol^{-1}
5β	Cyclopentane	134 000[d]	6.76	7 260	22.0
	Cyclohexane	129 000[d]	6.53	59 100	27.2
	Cycloheptane	135 000[d]	6.79	610 000	33.0
	Cyclooctane	133 000[d]	6.63	4 700 000	38.1
	Cyclopentanol	145 000[d]	7.31	877	16.8
	Cyclohexanol	162 000[d]	8.08	3 880	20.5
	Cycloheptanol	151 000[d]	7.60	22 500	24.8
	Cyclooctanol	144 000[d]	7.28	64 400	27.4
	Cyclononanol	137 000[d]	6.86	94 000	28.4

[a] Sensitivity factor (a) is the proportional coefficient of eqn. (3); see text. [b] Ultimate $\Delta\Delta\varepsilon$ value obtained by extrapolating eqn. (5) to $[G]_0 = 10$ mol dm^{-3}. [c] $[H]_0 = 50$ μmol dm^{-3} in H_2O, unless noted otherwise. [d] $[H]_0 = 25$ μmol dm^{-3}; in order to compensate for the concentration difference, the a value obtained was divided by 2 for comparison with the relevant values. [e] Measured in D_2O under comparable conditions, except for $[H]_0$. [f] $[H]_0 = 33$ μmol dm^{-3}; in order to compensate for the concentration difference, the a value obtained was divided by 1.5 for comparison with the relevant values.

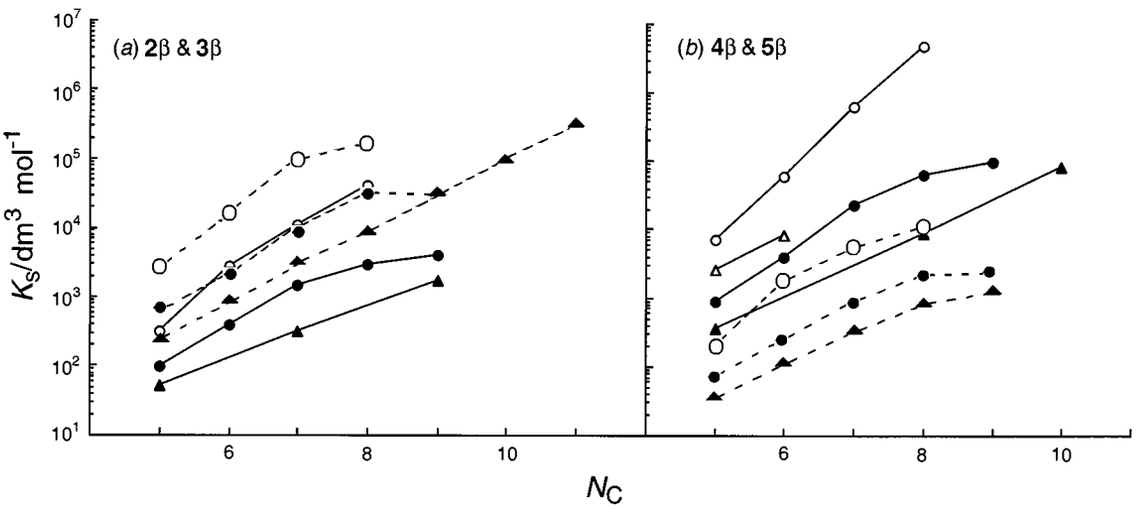


Fig. 8 Complex stability constant (K_s) plotted as a function of the number of methylenes (N_C) for the complexation of a series of alkanes (△), alkan-1-ols (▲), cycloalkanes (○) and/or cycloalkanols (●) with (*a*) **2**β (dotted lines) and **3**β (solid lines) and (*b*) **4**β (dotted lines) and **5**β (solid lines) in H_2O

β-Cyclodextrin phthalate, benzamide and naphthoate (3β–5β). These distinctly different substituents introduced to β-cyclodextrin led to considerable differences in complexation behavior. As shown in Table 2, the introduction of a methoxycarbonyl group at the *ortho* position of the tether benzoate group in **2**β causes a significant drop in the binding ability of **3**β. Thus, the K_s values decrease by at least one order of magnitude for all the guest series examined, without changing the profile of the N_C − log K_s plot, as shown in Fig. 8(*a*). These global decreases in binding affinity may be attributed to the steric hindrance of the *o*-methoxycarbonyl group embedded in the cavity, as well as the stronger intramolecular inclusion of the methyl phthalate moiety which competes with the guest for the cavity. This is demonstrated more clearly by NMR spectroscopy.

The assignment of **3**β's protons was achieved on the basis of the detailed analyses of the 2D-NMR spectra such as DQF-COSY, TOCSY and HMQC. First of all, a set of well resolved signals are assignable to the spin system of the glucose moiety substituted by the phthalate group. The signals of methylene protons (H-6) of the substituted glucose, which appear at very low field (δ 4.277 and 4.970) owing to the substitution by phthalate, are correlated with the signal of the carbon C-6 at δ 66.83 in the HMQC spectrum. Hence, the protons H-1–H-5 of the glucose are readily assigned to signals at δ 5.035, 3.654, 3.877, 3.483 and 4.035 respectively, using DQF-COSY and TOCSY spectra. Furthermore, the anomeric proton H-1′ at δ 5.085 of the glucose moiety adjacent to that substituted is assignable on the basis of the NOE contact with H-4 at δ 3.483 in the ROESY spectrum. Starting from H-1′, the assignments of H-2′ and H-3′ at δ 3.640 and 3.957 are in turn confirmed by scalar couplings of DQF-COSY and TOCSY spectra. The resonances for each proton at the relevant position of the remaining glucose residues in the cyclodextrin are almost degenerate and are assigned using an HMQC experiment as usual. The singlet methyl signal at δ 3.897, overlapping partly with the degenerate H-3′ and H-6′ protons, is attributed to the methoxy group in the phthalate ester as a result of the correlation with the methoxy carbon signal at δ 53.97. The inclusion of the methoxycarbonyl group in **3**β was elucidated by the ROESY technique. As can be seen from Fig. 9 (upper left corner), only one '*ortho*' proton (*o*-H′) in the phthalate moiety of **3**β shows appreciable NOE signals, one of which results from the NOE contact with cyclodextrin's H-5 and another, arising from interaction with the ester's methyl protons and/or cyclodextrin's H-3. The assignment of *o*-H′ rests on the upfield shift, which is a result of the steric compression induced by inclusion, and the NOE with the adjacent ester's methyl protons. From these data, we can deduce a conformation of **3**β as depicted in Fig. 9. The embedded methoxycarbonyl diminishes the effective cavity size and the methyl phthalate residue competes with guests for the cavity, both of which lead to greatly reduced complex stabilities for all guests examined in this study.

Of the native and modified cyclodextrins employed, benzoaminoethyl-β-cyclodextrin **4**β gave the lowest K_s values for all examined guests. Possessing a hydrophilic flexible tether connecting the cyclodextrin and aromatic moiety, **4**β shows a steady decrease in the CD intensity upon addition of guest,

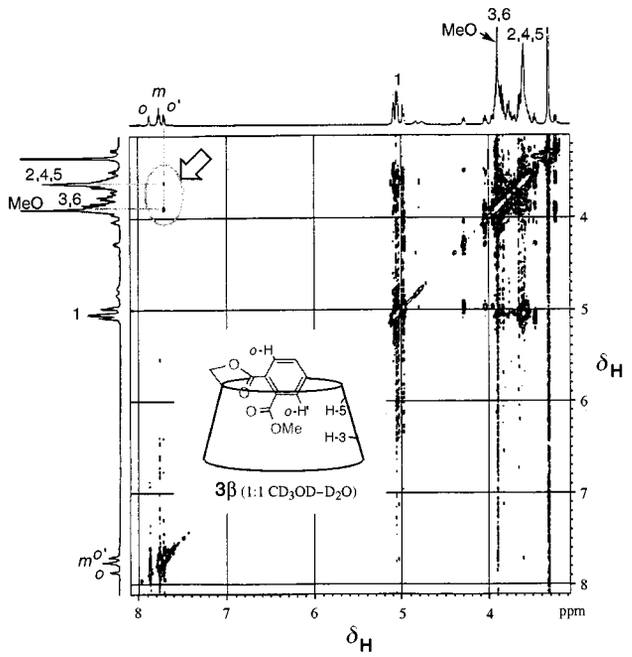


Fig. 9 ROESY spectrum with assignments and the elucidated conformation (inset) of **3**β in 1 : 1 CD_3OD–D_2O. The cyclodextrin protons are numbered.

ultimately affording an almost flat CD spectrum, as shown in Fig. 5(*a*). This CD spectral profile is completely different from those observed with the other cyclodextrin derivatives. Thus, the addition of a large amount of guest leads to the greatly enhanced CD intensities in the cases of **2**α and **2**β, or to a different-shaped final spectrum with decreased intensity, as is the case for **3**β and **5**β. The steady decrease in the CD intensity of **4**β at high guest concentrations means that, as a result of the competition between the substituent and a guest molecule, the chromophoric benzamide group is driven out of the cavity and out of the cyclodextrin's chiral field. The hydrophilic ethylenediamine tether may facilitate the total exposure of the aromatic substituent to the bulk water.

Conversely, cyclodextrin naphthoate **5**β affords the highest K_s values among the hosts used. Furthermore, this host does not show any saturation of K_s for cycloalkanes which have N_C values of at least 8, in contrast to the behavior of the other hosts that show saturation of K_s. This indicates again that the naphthyl group perching over the rim greatly expands the hydrophobic cavity. However, cycloalkanols do not seem to make use of this expanded cavity, since the hydroxy group does not allow full penetration of the cycloalkanol molecule. This rationalization is compatible with the much larger differences in K_s between (cyclo)alkanes and (cyclo)alkanols for **5**β than the K_s values observed for any of the other hosts. With **5**β, the K_s(cycloalkane)/K_s(cycloalkanol) ratio increases from 8.3 at $N_C = 5$ to 73 at $N_C = 8$.

Unit increment per methylene ($-d\Delta G°/dN_C$)

Since hydrophobic and van der Waals interactions are the major driving forces for guest inclusion by cyclodextrin, the log K_s, or $-\Delta G$, value does increase linearly with N_C until a certain limit, which depends on the host–guest combination employed, as demonstrated above. In order to evaluate quantitatively these contributions, the increments of $|\Delta G°|$ per methylene in a guest molecule are calculated from the linear regions of the N_C *vs.* log K_s plots shown in Figs. 7 and 8. The results are listed in Table 3, along with values reported for native cyclodextrins.[15]

It is intriguing that the unit increment is not appreciably affected by the modification or the size of the cyclodextrin host, but depends critically on the structure and functionality of the guest molecule. In general, acyclic guests give significantly smaller unit increments than cyclic guests, for which the less-efficient van der Waals interactions of the linear acyclic guests with the cyclodextrin cavity may be responsible. Although the mean unit increment for cycloalkanols (3.3 kJ mol^{-1}) is only moderately larger than that for alkanols (2.7 kJ mol^{-1}), the difference between alkanes (3.1 kJ mol^{-1}) and cycloalkanes (5.4 kJ mol^{-1}) amounts to 2.3 kJ mol^{-1}. However, it is reasonable to assume that cycloalkanes possessing the right size/shape and no hydrophilic group can gain the optimum stabilization upon inclusion. Therefore, we may conclude that this remarkably large unit increment observed for cycloalkanes (5.4 kJ mol^{-1}) represents the inherent $-\Delta G°$ value which can be obtained from the van der Waals interaction of one methylene group with the cyclodextrin cavity, and also that any hydrophilic group in a guest molecule prevents the guest residing at the most favorable position with a fully optimized structure.

Table 3 Unit increment of $\Delta G°$ per methylene ($-d\Delta G°/dN_C$) for some guest series in H_2O [a] (and in 1 : 1 CH_3OH–H_2O) [b]

	$-d\Delta G°/dN_C$			
Host	Alkane	Alkan-1-ol	Cycloalkane	Cycloalkanol
1α		3.0 [c]		
1β		3.1 [c]		3.5 [c]
2α	2.6	2.3		
2β	3.8 (1.6) [b]	2.9	5.2 (1.7) [b]	3.3
3β		2.2	5.3	3.4
4β		2.8	5.4	3.1
5β	2.9	2.7	5.5	3.4
Mean	3.1 ± 0.6	2.7 ± 0.3	5.4 ± 0.1	3.3 ± 0.2

[a] Evaluated from the linear regions of N_C *vs.* log K_s plots in Figs. 7 and 8. [b] Ref. 9; unit increment determined in 1 : 1 CH_3OH–H_2O. [c] Ref. 14.

The $-d\Delta G°/dN_C$ values obtained above for cyclodextrin complexation may be compared with the corresponding values calculated from the unit increments (per methylene) for the solubility of pure alkanes, alkanols and cycloalkanes in water,[16] the critical micelle concentrations of various surfactants[16,17] and the solubility of pure alkanes in micelle.[17] The $-d\Delta G°/dN_C$ values evaluated from the solubility of alkanes ($N_C = 4$–8), alkanols ($N_C = 4$–10) and (methyl)cycloalkanes ($N_C = 5$, 6) in water are 3.7, 3.4 and 3.1 kJ mol^{-1}, respectively.[16] Non-ionic ($N_C = 8$–12) and zwitterionic ($N_C = 10$–16) surfactants give somewhat smaller unit increments of 2.8–2.9 kJ mol^{-1}, although cationic ($N_C = 10$–16 or 18) and anionic ($N_C = 8$–14) surfactants afford considerably decreased values of 1.7–1.8 kJ mol^{-1}.[17] More interestingly, the $-d\Delta G°/dN_C$ value obtained from the solubility of alkanes ($N_C = 2$–5) in sodium dodecylsulfate micelle in aqueous solution is 3.2 kJ mol^{-1}.[16] These unit increments reported are very close to those obtained in the present study for alkanols (2.7 kJ mol^{-1}), alkanes (3.1 kJ mol^{-1}) and cycloalkanols (3.3 kJ mol^{-1}), indicating that these molecular association processes share the same major contributions of the hydrophobic and van der Waals interactions. In this context, the particularly large $-d\Delta G°/dN_C$ value of 5.4 kJ mol^{-1} obtained in the complexation of cycloalkanes with β-cyclodextrins may need further justification. In addition to the enhanced van der Waals interactions due to the deeper penetration and/or closer contact within the cyclodextrin cavity, some entropic gains arising from the originally restricted cyclic structure of the host and guest—compared with the acyclic counterparts—may also be responsible for the higher unit increments for the cyclic guests.

Isotope effects

The complexation behavior of cyclodextrins is often evaluated, in deuterated solvents in particular, by NMR spectroscopic

Table 4 Sensitivity factor (α),[a] ultimate change in CD ($\Delta\Delta\varepsilon_{max}$),[a] complex stability constant (K_s), enantioselectivity (K_s^+/K_s^-), free energy change ($\Delta G°$) and differential free energy change ($\Delta\Delta G°$) for inclusion complexation of modified cyclodextrins with some chiral alcohols in H_2O at 25 °C

Host	Guest	α[a]	$\Delta\Delta\varepsilon_{max}$[a]	K_s/dm^3 mol^{-1}	K_s^+/K_s^-	$-\Delta G°$/kJ mol^{-1}	$\Delta\Delta G°$/kJ mol^{-1}
2α	(*S*)-(+)-Octan-2-ol	26 700	1.34	2 730	0.95	19.6	−0.1
	(*R*)-(−)-Octan-2-ol	27 800	1.39	2 860		19.7	
2β	(*S*)-(+)-Octan-2-ol	31 500	1.56	4 770	1.03	21.0	+0.1
	(*R*)-(−)-Octan-2-ol	31 200	1.56	4 650		20.9	
	(+)-Limonene	22 800	1.14	171 000	1.28	29.9	+0.7
	(−)-Limonene	21 600	1.08	134 000		29.2	
	(+)-Menthol	38 700	1.96	58 000	2.00	27.2	+1.7
	(−)-Menthol	33 900	1.73	29 000		25.5	
	(+)-Borneol	46 100	2.31	172 000	0.84	29.9	−0.4
	(−)-Borneol	45 400	2.27	205 000		30.3	
3β	(+)-Menthol	67 700	3.39	1 920	1.00	18.7	0.0
	(−)-Menthol	63 400	3.17	1 920		18.7	
	(+)-Borneol	71 500	3.58	20 600	1.11	24.6	+0.2
	(−)-Borneol	75 400	3.77	18 600		24.4	
4β	(*S*)-(+)-Octan-2-ol	93 500	4.58	398	1.00	14.8	0.0
	(*R*)-(−)-Octan-2-ol	96 500	4.71	399		14.8	
	(+)-Menthol	108 000	5.27	1 950	0.86	18.8	−0.3
	(−)-Menthol	105 000	5.14	2 260		19.1	
5β	(+)-Menthol	276 000	6.89	40 200	1.04	26.3	+0.1
	(−)-Menthol	304 000	7.59	38 700		26.2	

[a] See footnotes of Table 2.

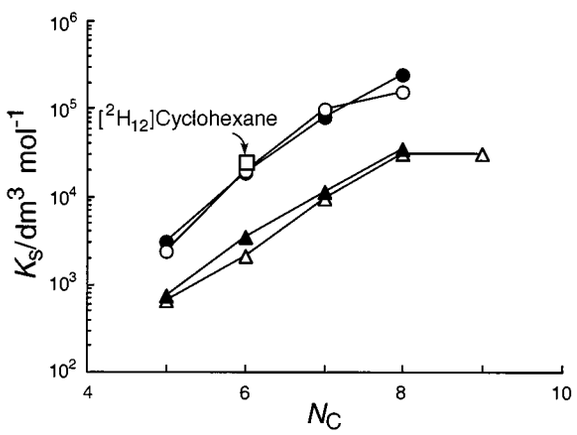


Fig. 10 Complex stability constant (K_s) plotted as a function of the number of methylenes (N_C) for complexation of **2**β with a series of cycloalkanes in H_2O (○) and D_2O (●), cycloalkanols in H_2O (△) and D_2O (▲), and for [$^2H_{12}$]cyclohexane (□) in H_2O

techniques, and the complex stability constants (K_s) are believed not to be affected significantly by the deuterated solvents. However, a direct comparison of K_s in D_2O and H_2O has not been performed until recently and the results reported appear inconsistent with each other.[18–21]

K_s values in H_2O are reported to be appreciably smaller than the corresponding values in D_2O in the complexation of native[19] and modified[18] α- and β-cyclodextrins with some neutral or anionic aromatic molecules (*p*-nitrophenol, *p*-nitrophenolate, methyl orange and phenolphthalein),[19] as well as with lipophilic inorganic anions (I^-, SCN^- and ClO_4^-).[18,19] Interestingly, the $K_s(H_2O)/K_s(D_2O)$ ratios remain more or less constant (0.79 ± 0.05), irrespective of the host and guest used. The higher binding constants observed in D_2O have been ascribed to stronger hydrophobic and electrostatic interactions, caused by the more ordered solution structure of D_2O (arising from stronger hydrogen bonds), and its slightly smaller relative permittivity respectively.[19]

However, contradictory results have been reported for the complexation of a series of alkanedioates (N_C = 8–11) with α-cyclodextrin.[20,21] Thus, the K_s values for N_C = 9–11 alkanedioates determined by calorimetry in H_2O[21] are generally in good agreement with those determined by NMR titration in D_2O,[20] although when octanedioate is used as a guest, an appreciably higher K_s value is reported in D_2O than in H_2O.

Since the present systems involve simpler guest molecules, it is interesting to examine the deuterium isotope effects of both solvent and guest molecule upon the complexation behavior of cyclodextrin derivative **2**β. The hydrogen-bonding interaction, if involved in any way in the complexation process, should be significantly affected by the use of a deuterated solvent, while the van der Waals and hydrophobic interactions should be influenced by deuteration of the guest.

The complex stability constant K_s for cycloalkanes and cycloalkanols was determined in deuterated water, and the results are listed in Table 2. The K_s values obtained in D_2O and H_2O are plotted as functions of N_C in Fig. 10. Although the solubilities of **2**β and its complexes appear to be slightly lower in D_2O than in H_2O, the K_s values for cycloalkanes and cycloalkanols are essentially identical in both solvents, within experimental error (±0.15 kJ mol^{-1} in $\Delta G°$). This clearly indicates that the possible hydrogen-bonding interactions of the peripheral hydroxy groups of cyclodextrin with the guest's hydroxy group do not significantly influence the inclusion complexation or, more probably, are totally absent. That no solvent isotope effect is observed here is consistent with the results obtained for alkanedioates,[20,21] but conflicts with results reported for aromatic and inorganic guests.[18,19] It is likely that hydrophobic contributions are much more predominant in the complexation of the latter guests, although further work is needed to come to a definite conclusion on this matter.

Somewhat unexpectedly, the deuteration of guest cyclohexane did not appreciably alter the complex stability with **2**β. The deuterium isotope effect upon van der Waals interaction has been evaluated by the variational calculations of vibrational energies with van der Waals trimers of Ar_2–HX and Ar_2–DX, where X = F or Cl.[22] These calculations have revealed that the bonding energies of Ar_2–HF and Ar_2–HCl are very close to those of Ar_2–DF and Ar_2–DCl, irrespective of the model employed. In the 'total-1' mode, which takes into account the non-additive forces, the binding energies calculated for Ar_2–HF and Ar_2–DF (v = 0) are 277 and 291 cm^{-1}, while those calculated for Ar_2–HCl and Ar_2–DCl (v = 0) are 312 and 321 cm^{-1}. In these systems which involve highly polar HX molecules, the non-additive forces arise from contributions both from dispersion and induction, and the calculations refer to the vapor phase.[22] Hence, a direct comparison with the van der Waals interactions within the cyclodextrin cavity is difficult

and perhaps invalid, yet it is not altogether surprising that no appreciable isotope effect is observed upon complexation of [$^2H_{12}$]cyclohexane in the present study, where only dispersion forces contribute to the van der Waals interaction.

Chiral recognition

Since the cyclodextrin cavity is inherently chiral, the complexation behavior of **2**α–**5**β was also examined with some representative optically active guests, and the results are shown in Table 4. Although the enantiomers of some cyclic guests are discriminated appreciably by the cyclodextrin derivatives **2**α–**5**β, the observed enantioselectivities, defined by the ratio of stability constants (K_s^+/K_s^-), are relatively low in most cases, as has been demonstrated for the other cyclodextrin derivatives.[23] In general, the enantiomers of acyclic guests, such as octan-2-ol, are very difficult to discriminate between, even by the α-cyclodextrin derivative **2**α. Among the cyclodextrins examined, **2**β gave the highest enantioselectivity (K_s^+/K_s^-) of 2.0 with menthol.

Although it seems somewhat speculative to extract a general conclusion from the limited data available, a close examination of the host structure and the enantioselectivity suggest that the substituents, which reduce the original cavity space, tend to lower any complex stability as well as enantioselectivity. Typically, the complexation of **2**β with enantiomeric menthols may be compared with those of **3**β and **4**β. The latter two hosts, possessing deeply penetrating chromophores, afford much smaller complex stabilities and enantioselectivities than **2**β. This result seems reasonable, since weak binding, leading to shallow inclusion, is not enough to produce an appreciable difference in K_s for enantiomers.

Acknowledgements

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