Carbohydrate Research, 125 (1984) 65–76
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

N.M.R. STUDIES OF CYCLOAMYLOSE INCLUSION-COMPLEXES WITH *p*-SUBSTITUTED PHENOLS

YOSHIO INOUE*, TAKEHIRO OKUDA, YOSHIAKI MIYATA, AND RIICHIRO CHÛJÔ

Department of Polymer Chemistry, Tokyo Institute of Technology, O-okayama 2-chome, Meguro-ku, Tokyo 152 (Japan)

(Received May 4th, 1983; accepted for publication, July 26th, 1983)

ABSTRACT

Aqueous solutions of inclusion complexes of host cyclomaltohexa- and cyclomaltohepta-ose (cyclohexa- and cyclohepta-amylose) with guest phenols *p*-substituted with Br, Cl, CN, NO_2, CH_3, CHO, and COOH have been studied by ^{1}H- and ^{13}C-n.m.r. spectroscopy. The stability of the complexes depends on the guests, the cycloamyloses, and the ionisation states of the host hydroxyl groups. The ^{1}H data for the host protons in the complexes show that the guests are more deeply inserted into the cavity of cyclomaltoheptaose than into that of cyclomaltohexaose.

INTRODUCTION

The cycloamyloses (cyclodextrins, CD) are cyclic oligosaccharides composed of at least six (1→4)-linked α-D-glucosyl residues. Each CD molecule has a toroidal, hollow, truncated cone with primary and secondary hydroxyl-groups crowning the narrower and wider rims, respectively. The interior of the cavity of each CD contains two rings of C-H groups and a ring of glucosidic oxygens. Hence, the interior of the cavity is relatively hydrophobic, whereas the exterior is relatively hydrophilic.

Each CD can admit various guest molecules into the cavity, without any covalent bonds being formed[1–3] and, consequently, cycloamyloses have been utilised as models for enzymic catalysis[1–4] and for a variety of other purposes[3–5]. The kinetics and mechanisms of numerous CD-catalysed stereospecific reactions have been studied[1–4] and investigations of the molecular geometry of CD inclusion-complexes in solution are therefore important. Little is known of this geometry, in particular the position of the guest in the cavity[6,7], although there are many data on the formation of inclusion complexes in aqueous solution[1–3,8–19] and some inclusion complexes have been investigated by X-ray crystallography[20–25]. The geometry of CD inclusion-complexes in the solid state is not necessarily the same as that in solution[26,27].

---

*To whom inquiries should be addressed.

0008-6215/84/$ 03.00

We have investigated aqueous solutions of CD inclusion-complexes with *p*-substituted phenols by ^{1}H- and ^{13}C-n.m.r. spectroscopy. *p*-Substituted phenols give simple ^{1}H-n.m.r. spectra and have suitable solubility.

Space-filling (Corey–Pauling–Koltun) models suggest that cyclomaltoheptaose (cyclohepta-amylose, β-CD) can form inclusion complexes with *p*-substituted phenols which are more stable than those formed by cyclomaltohexaose (cyclyhexa-amylose, α-CD), and in which the aromatic ring of the phenol is more deeply inserted into the cavity. Since both CD and the *p*-substituted phenols have ionisable hydroxyl groups, with pK_a values of ~12.1[28] and 7.0–10.0[29], respectively, it is of interest to study the pH dependence of the stability and the molecular geometry of the inclusion complex.

EXPERIMENTAL

Materials. -- The α-CD, β-CD, and all *p*-substituted phenols were commercial materials, and ^2H_2O (isotopic purity 99.7%), ^2HCl (38%), NaO^2H (40%), and $^2H_3PO_4$ (85%) were used. For investigating the effect of the medium pH on the complex formation, the following solvents were used: *A*, M NaO^2H (all hydroxyl groups ionised); *B*, phosphate buffer, p^{2}H 11 [for *p*-bromophenol (PBP), *p*-chlorophenol (PClP), *p*-hydroxybenzoic acid (PHBA), and *p*-cresol (PMP)]; *C*, phosphate buffer, p^{2}H 10.0 [for *p*-cyanophenol (PCP), *p*-hydroxybenzaldehyde (PCHO), and *p*-nitrophenol (PNP)]; *D*, phosphate buffer, p^{2}H 7.0 (for PBP, PClP, PHBA, and PMP); and *E*, phosphate buffer, p^{2}H 6.0 (for PCP, PCHO, and PNP). The choice of these p^{2}H values was based on the pK_a values of the various phenols. In solvents *B* and *C*, only the hydroxyls of the guests were ionised; in *D* and *E*, almost all of the hydroxyls were not ionised. The buffers *B*–*E* were made up with $^2H_3PO_4$ and Na_3PO_4, and the ionic strength was adjusted to ~0.5.

Methods. -- Proton-decoupled, ^{13}C-n.m.r. spectra were recorded with a JEOL JNM PS-100 spectrometer (25 MHz), using a spectral width of 4000 Hz and 4096 data points (resolution 2.0 Hz). ^{1}H-N.m.r. spectra were recorded with JEOL JNM PS-100 (100 MHz) and FX-270 spectrometers (270 MHz), using sweep widths of 1000 Hz (4096 data points, resolution 0.5 Hz) and 1350 Hz (8192 points, resolution 0.3 Hz), respectively. The chemical shifts of the ^{1}H and ^{13}C signals were measured in p.p.m. downfield from that of external Me_4Si, and assignments were based on literature data[6,8,13]. U.v. absorption spectra were recorded with a Beckman-25 spectrometer. All spectroscopic measurements were made at 31 ±1°. The p^{2}H values, obtained by adding 0.4 to the reading of the pH meter to correct for isotopic effects[30], were determined using a Toko model TP-101 pH-meter with a micro combination-electrode CE103.

Dissociation constants K_d for CD complexation were obtained (*a*) from changes in u.v. spectra induced by complexation (average of several K_d values determined at different wavelengths; this method could not be used for alkaline solutions, because of the large absorption of the alkoxide anion); (*b*) using a ^{1}H-n.m.r.

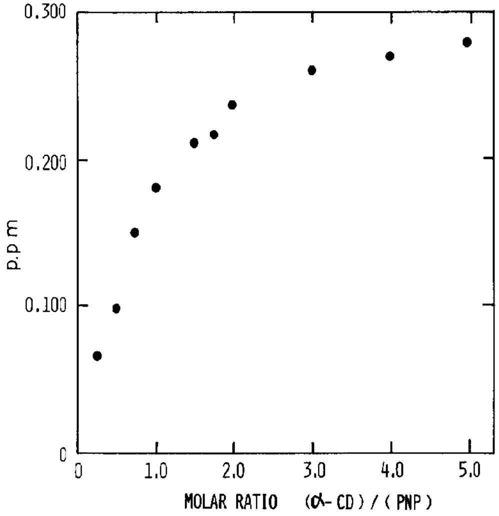


Fig. 1. ^{1}H-Chemical shift displacements of the lower-field doublet of aromatic resonances of *p*-nitrophenol (PNP) on addition of α-CD in phosphate buffer of p^{2}H 6; [PNP] 0.01M.

titrational technique, *i.e.*, ^{1}H chemical shifts of guests as a function of CD concentration (Fig. 1). The K_d value was derived by least-squares fitting of the modified Hildebrand–Benesi equations[6,31,32] to the chemical shifts *vs* concentration curve. This method cannot be used for β-CD complexation at low p^{2}H values because of the low solubility of β-CD and the consequent low n.m.r. signal-to-noise ratio under these conditions. For an accurate determination of K_d, ^{1}H-spectra have to be measured for a relatively wide range of [CD]/[guest] ratios. It was assumed that a 1:1 complex between CD and the guest was formed and that complexation was reversible.

The most probable (time-averaged) position of the guests in the CD cavity in an aqueous solution was determined by fitting the intrinsic chemical-shifts ($\Delta\delta_{int}$) of H-3 and H-5 of CD to those reflecting the ring-current effect of the aromatic ring of the guests and calculated using the Johnson–Bovey equation[33]. Here, $\Delta\delta_{int}$ is defined as $\delta_b - \delta_o$, where δ_b and δ_o are the chemical shifts in the fully complexed and uncomplexed states, respectively. As an example, Fig. 2 shows the ^{1}H-n.m.r. spectral changes of α-CD by complexation with PNP in buffer solution of p^{2}H 6.0. The values of δ_b and thus of $\Delta\delta_{int}$ were estimated from the chemical shifts at known concentrations of CD and guests, in conjunction with the pre-determined K_d values.

The procedure for determining the most probable position has been described in detail[6,7]; briefly, it involves the following assumptions. (*1*) α-CD and β-CD have hexagonal and heptagonal symmetries in solution, respectively, and the respective H-3 and H-5 located inside the cavity form rings with radii of 3.6 (H-3) and 3.2 Å (H-5) for α-CD, and 4.1 (H-3) and 3.5 Å (H-5) for β-CD. The centres of the ring for H-3 and H-5 are on the symmetry axes of the CD cavity and the

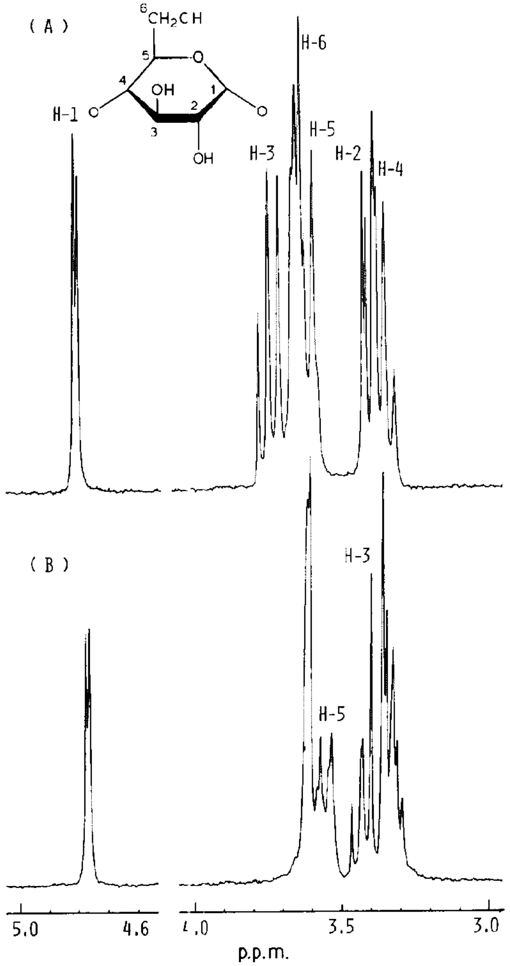


Fig. 2. ^{1}H-N.m.r. spectra (270 MHz) of (A) free α-CD (0.01M) and (B) α-CD (0.01M)–PNP (0.05M) in phosphate buffer of p^{2}H 6.

centre-to-centre distance is 2.5 Å for each CD. These values were based on space-filling molecular models. (*2*) H-3 and H-5 of CD are shielded due to the ring-current effects of the included phenols, where the twofold axis of guests coincides with the symmetry axis of the CD cavity. The shielding and/or deshielding effects by the phenol substituents were ignored[6,7]. (*3*) The magnitudes of the ring-current effects on the respective H-3 and H-5 are the time-average[6,7] of those for several orientations of the aromatic plane with respect to H-3 and H-5. This assumption is justified by the appearance of only one set of H-3 and H-5 resonances with the time-average chemical shifts, even for the CD inclusion-complexes at higher [guest]/[CD] ratio (Fig. 2). This assumption is supported by the ^{13}C relaxation-times, which indicated the occurrence of rapid rotation of the phenyl compounds in the cavity of α-CD and β-CD in solution[10,11,31,34,35].

The magnitude of the ring-current effects on H-3 and H-5 was then calculated as a function of the position of the centre of the aromatic ring in the cavity. The most probable position of the included guests in the cavity is that at which both observed H-3 and H-5 intrinsic chemical-shifts show maximal agreement with the calculated ring-current shifts. If the difference between the observed and calculated shifts was much larger than the probable experimental error, the estimate was discarded and one or more of the above assumptions must be regarded as inadequate. All calculations were made on a Sharp PC 1211 minicomputer.

RESULTS

Tables I and II contain the values of the dissociation constants K_d, intrinsic chemical-shifts ($\Delta\delta_{int}$) for H-3 and H-5 of CD for the complexes of α-CD and β-

TABLE I

DISSOCIATION CONSTANTS (K_d), ^{1}H INTRINSIC CHEMICAL-SHIFTS ($\Delta\delta_{int}$), AND PROBABLE POSITIONS OF GUESTS FOR α-CD INCLUSION-COMPLEXES IN AQUEOUS SOLUTION

Solvent[a]	*Guest*	K_d (M)	$\Delta\delta_{int}$ *(p.p.m.)*[b]		*Position (Å)*[c]
			H-3	*H-5*	
A	PBP	9.5×10^{-3}	−0.01	0.17	—[e]
	PClP	2.4×10^{-2}	0.05	0.14	—[e]
	PHBA	N.b.[d]	—[e]	—[e]	—[e]
	PMP	1.3×10^{-2}	0.05	0.00	—[e]
	PCP	2.0×10^{-2}	−0.03	0.04	—[e]
	PCHO	7.5×10^{-3}	0.05	0.03	—[e]
	PNP	4.5×10^{-3}	−0.09	0.08	—[e]
B	PBP	5.0×10^{-3}	−0.32	0.28	—[e]
	PClP	3.5×10^{-3}	−0.25	0.06	−0.3 ±0.3
	PHBA	8.2×10^{-2}	−0.86	0.31	—[e]
	PMP	2.4×10^{-2}	−0.23	−0.02	−0.2 ±0.1
C	PCP	4.4×10^{-3}	−0.29	0.06	−0.3 ±0.3
	PCHO	8.8×10^{-3}	−0.25	0.02	0.2 ±0.2
	PNP	1.3×10^{-3}	−0.26	0.02	0.0 ±0.1
D	PBP	6.8×10^{-3}	−0.32	0.21	—[e]
	PClP	7.9×10^{-3}	−0.31	0.04	−0.1 ±0.1
	PHBA	5.0×10^{-2}	−0.68	0.23	—[e]
	PMP	1.4×10^{-2}	−0.24	0.02	0.2 ±0.3
E	PCP	3.4×10^{-3}	−0.27	0.06	−0.3 ±0.3
	PCHO	1.5×10^{-2}	−0.28	0.06	−0.3 ±0.3
	PNP	2.5×10^{-3}	−0.33	−0.05	0.1 ±0.2

[a] A, M NaO^2H; B–E, phosphate buffers of p^2H 11.0, 10.0, 7.0, and 6.0, respectively. [b] Negative values indicate upfield shifts. [c] Distance between the center of the phenyl ring of the guest and the plane comprised of six H-3 of α-CD. Negative values indicate the direction towards the outside of the cavity. [d] No binding. [e] Not determined.

TABLE II

DISSOCIATION CONSTANTS (K_d), ^{1}H INTRINSIC CHEMICAL-SHIFTS ($\Delta\delta_{int}$), AND PROBABLE POSITIONS OF GUESTS FOR β-CD INCLUSION-COMPLEXES IN AQUEOUS SOLUTION

Solvent[a]	*Guest*	K_d (M)	$\Delta\delta_{int}$ *(p.p.m.)*[b]		*Position (Å)*[c]
			H-3	*H-5*	
A	PBP	9.3×10^{-3}	0.01	0.00	—[e]
	PClP	N.b.[d]	—[e]	—[e]	—[e]
	PHBA	N.b.[d]	—[e]	—[e]	—[e]
	PMP	3.0×10^{-2}	0.01	0.04	—[e]
	PCP	8.0×10^{-3}	0.04	0.05	—[e]
	PCHO	6.5×10^{-3}	0.05	0.07	—[e]
	PNP	3.7×10^{-3}	0.05	0.08	—[e]
B	PBP	4.0×10^{-3}	−0.08	−0.18	1.5 ±0.3
	PClP	8.3×10^{-3}	−0.08	−0.21	1.7 ±0.1
	PHBA	1.8×10^{-2}	−0.18	−0.28	—[e]
	PMP	7.5×10^{-3}	−0.10	−0.23	1.6 ±0.1
C	PCP	2.1×10^{-3}	−0.13	−0.19	1.3 ±0.1
	PCHO	5.9×10^{-3}	−0.15	−0.23	1.3 ±0.4
	PNP	1.5×10^{-3}	−0.13	−0.16	1.2 ±0.1
D	PBP	2.8×10^{-3}	−0.07	−0.19	1.6 ±0.3
	PClP	3.9×10^{-3}	−0.07	−0.20	1.7 ±0.2
	PHBA	4.0×10^{-2}	−0.16	−0.26	—[e]
	PMP	4.8×10^{-3}	−0.09	−0.23	1.7 ±0.01
E	PCP	2.9×10^{-3}	−0.13	−0.20	1.3 ±0.1
	PCHO	7.0×10^{-3}	−0.15	−0.24	1.4 ±0.4
	PNP	3.9×10^{-3}	−0.15	−0.24	1.4 ±0.4

[a] A, M NaO^2H; B–E, phosphate buffers of p^2H 11.0, 10.0, 7.0, and 6.0, respectively. [b] Negative values indicate upfield shifts. [c] Distance between the center of the phenyl ring of the guest and the plane comprised of seven H-3 of β-CD. Negative values indicate the direction towards the outside of the cavity. [d] No binding. [e] Not determined.

CD, respectively, and the most probable positions of the guests in the CD cavity, determined by comparison of the observed $\Delta\delta_{int}$ with the calculated ring-current shifts. The origin of the coordinate is the plane containing H-3 of each of the six (α-CD) or seven (β-CD) D-glucosyl residues, and the positive sign corresponds to the direction H-3→H-5 planes.

Table III contains the ^{13}C intrinsic chemical-shifts (defined as for ^{1}H) of guests in the α-CD complexes. Those for the β-CD complexes could not be determined accurately because of the low solubility of β-CD.

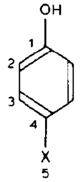
The dissociation constants for the systems α-CD/PHBA, β-CD/PHBA, and β-CD/PClP in M NaO^2H could not be determined, since the induced ^{1}H chemical-shifts were zero even at the highest [CD]/[guest] ratio (5.0) where [guest] was kept at 1.0×10^{-2}M. The formation of inclusion complexes should not occur in these systems.

TABLE III

INTRINSIC ^{13}C CHEMICAL-SHIFT DISPLACEMENTS OF GUEST COMPOUNDS INDUCED BY COMPLEXATION WITH α-CD IN AQUEOUS SOLUTION

Solvent[a]	*Guest*	*Carbon*[b]					
		1	*2*	*3*	*4*	*5*	*E.e.*[c]
A	PBP	−0.05	−0.60	0.44	−0.14	—	±0.10
	PClP	0.00	−0.65	0.57	−0.18	—	±0.13
	PMP	−0.06	−0.64	0.23	−1.32	0.52	±0.12
	PCP	0.68	−0.13	0.81	−1.31	−0.69	±0.13
	PNP	0.72	−0.16	1.78	−0.72	—	±0.11
B	PBP	3.32	0.24	0.35	−2.38	—	±0.12
	PClP	2.11	−1.88	0.44	0.00	—	±0.11
	PHBA	4.13	−1.00	0.83	−0.60	−0.70	±0.25
	PMP	1.42	0.18	0.09	−2.13	1.06	±0.18
C	PCP	0.58	0.80	−0.05	−2.70	−0.32	±0.11
	PNP	3.54	0.55	1.16	−1.97	—	±0.10
D	PBP	1.08	−0.54	0.41	−3.24	—	±0.13
	PClP	0.95	−0.88	0.49	−0.31	—	±0.13
	PHBA	0.48	−0.96	1.84	0.10	−0.58	±0.20
	PMP	0.71	0.00	0.14	−0.63	1.01	±0.16
E	PCP	1.82	0.48	−0.12	−0.17	−0.53	±0.11
	PNP	5.82	0.91	−1.65	−3.03	—	±0.10

[a] A, M NaO^2H; B–E, phosphate buffers of p^2H 11.0, 10.0, 7.0, and 6.0, respectively. [b] Chemical shifts are expressed as p.p.m. Numbering of carbon atoms for guest compounds is as shown below. [c] Experimental error.



For all systems in M NaO^2H and for PHBA-containing systems in buffer solutions, the probable position of the phenyl ring at which both observed H-3 and H-5 intrinsic chemical-shifts coincided with the corresponding ring-current shifts could not be found.

Formation and stability of the inclusion complexes. — From the data presented above, it is clear that the CD–guest systems form 1:1 inclusion complexes in the different media, with a few exceptions in M NaO^2H. The stability of complexes depends on the CD, guest, and solvent. For many systems, the complexes in buffers *B–E* are slightly more stable than those in M NaO^2H, as judged from the K_d values. An extreme case is PHBA, which did not form stable inclusion complexes with α-CD and β-CD in M NaO^2H. PHBA complexation was observed in the buffer solutions, but the stability was relatively low, possibly because of the carboxylate anion. It is not clear why PClP did not form a stable inclusion complex with β-CD in M NaO^{2}H, but formed one with α-CD in the same solvent, whereas the related compound PBP formed a stable complex with β-CD even in M NaO^{2}H.

The K_d values for these systems in buffers B and C are different from those in buffers D and E, but their relative magnitudes are not systematically related to the identity of the guest or CD. There are no clear trends in the difference of K_d values for the α-CD and β-CD complexes for a given guest in a given solvent.

Molecular geometry of the inclusion complexes. — For each of the complexes, the relative magnitude and the sign of $\Delta\delta_{int}$ for H-3 and H-5 clearly demonstrate that the phenyl rings are inserted into the CD cavity in the same manner as observed in many other complexes[1–3], namely, from the secondary-hydroxyl side of CD. There are two possibilities for the guest insertion, namely, insertion with the *p*-substituent or the hydroxyl group in the lead. Earlier ^{13}C-n.m.r. studies of α-CD complexes with substituted benzenes, including *p*-substituted phenols, showed that the included lead (ipso) carbons are largely shielded as compared with the deshielding of corresponding *p*-carbons[13,32,36]. On this basis, in different media, the guests are inserted into the α-CD cavity with the *p*-substituents in the lead (see Table III). These observations are consistent with previous findings[6,8,9,13,24,32,36] for solutions as well as for the solid state.

Since ^{1}H-n.m.r. studies[7,9] have shown that *p-tert*-butylphenol and sodium *p*-nitrophenoxide also penetrate into the β-CD cavity with the non-phenolic substituents leading, it is reasonable to assume that all guests investigated here behave likewise. The nature of the lead substituent does not influence the determination of the probable position of the phenyl ring in the cavity.

For α- and β-CD complexes in M NaO^{2}H, the estimated $\Delta\delta_{int}$ values for H-3 and H-5 did not agree in magnitude or sign with the calculated ring-current shifts, probably because of inappropriate assumptions in the calculation. In M NaO^{2}H, the CD hydroxyl-groups are ionised, so that intramolecular hydrogen bonds involving HO-2,3 are broken and the α- and β-CD rings are distorted due to the repulsive interaction of adjacent anions. The absolute values of $\Delta\delta_{int}$ for H-3 of α-CD and β-CD in M NaO^{2}H solution are small compared with the corresponding values in buffer solutions, suggesting that the secondary-hydroxyl end of the CD ring is widened by the repulsion. It is concluded that the guest phenols stay at almost the same position in the cavity in buffer solutions; the centres of the phenyl rings are located at ~ -0.1 Å in the α-CD cavity and at $\sim +1.4$ Å in the β-CD cavity independent of the *p*-substituents and pH of the buffer solvents, where the zero position is on the H-3 plane and the positive direction is from the secondary-hydroxyl end to the inside of cavity. Although the most probable position of PHBA in the α- and β-CD cavities in buffer solutions could not be determined, it is not unreasonable to deduce from the magnitudes of $\Delta\delta_{int}$ for H-3 and H-5 that PHBA also stays at a position which is almost identical to that of the other guests in the β-CD cavity. Fig. 3 illustrates the most probable positions for the *p*-substituted phenols in the α- and β-CD cavities. The centre of the phenyl ring is approximately on the H-3 plane for

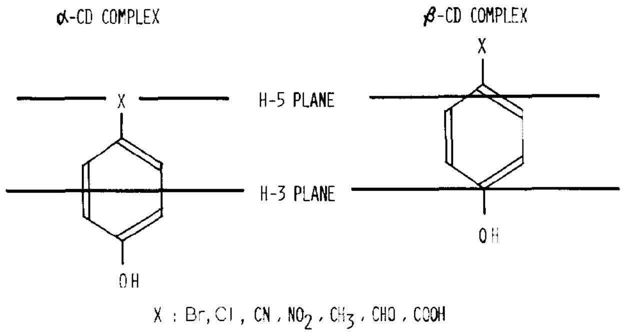


Fig. 3. The most probable geometry of α-CD and β-CD inclusion-complexes with *p*-substituted phenols in aqueous solution.

the α-CD complexes and approximately half-way between the H-3 and H-5 planes for the β-CD complexes.

DISCUSSION

For the *p*-substituted phenols investigated, many of their inclusion complexes with α-CD and β-CD are less stable in M NaO^2H than in phosphate buffers, indicating that the stability depends on the extent of ionisation of the CD hydroxyl-groups, the ionisation of the hydroxyl group of the phenol being less important. Ionisation of the CD hydroxyl-groups destroys the interglucosidic, intramolecular hydrogen bonds involving HO-2,3 which confer rigidity on the CD molecule. Since methylated cyclomaltohexa- and cyclomaltohepta-oses, which have geometric properties similar to those of α-CD and β-CD but differ primarily in hydrogen-bonding capability and polarity, can form stable inclusion complexes with benzenoid compounds in aqueous solution[37,38], the destabilisation of the complexes involving α- and β-CD cannot be related directly to the destruction of the hydrogen bonds. The ionisation of hydroxyl groups may result in widening of the circle of secondary hydroxyl groups in the CD cavity due to repulsive interaction of the ionised hydroxyl groups. Increased flexibility of the CD macrocycle in M NaO^2H has been confirmed by the ^{13}C spin–lattice relaxation-time[31]. An increased width of the secondary-hydroxyl end of the macrocycle was suggested by the smallness of $\Delta\delta_{int}$ values for H-3 of α-CD and β-CD in M NaO^2H as compared with those in the buffer solutions.

Space-filling models suggest that widening of the secondary-hydroxyl end induces the narrowing of the opposite end and, hence, shallowing of the cavity. Thus, the destabilisation of the complexes associated with ionisation of the CD hydroxyl-groups may be attributable to the destruction of the stable hydrophobic cavity of CD. The finding that PHBA could not form stable inclusion complexes in M NaO^2H may be also explained in this way, since, in buffer solutions, it forms stable inclusion complexes in which the carboxylate group is located in the cavity.

The insensitivity of the stability of the inclusion complexes to the ionisation of phenolic hydroxyl groups can be explained on the basis of the molecular geometry proposed above. The electrostatic interaction and the hydrogen bonding between the hydroxyl groups or hydroxide anions of CD and phenolic compounds are expected to disturb or stabilise the complexes, respectively[31]. Space-filling models suggest that the most probable position of the guest phenolic compounds is as shown in Fig. 3, with the phenolic hydroxyl groups too remote to interact with the peripheral hydroxyl groups of α-CD and fully exposed to the solvent. This situation also applies to β-CD complexes, in which the guests penetrate more deeply into the cavity. In contrast, the ionised group included in the cavity destabilises the complex, as can be seen in the K_d values for the PHBA complexes.

For all of the CD–guest systems, the phenolic rings penetrate up to almost the same position in the CD cavity at 100% binding, irrespective of the type of *p*-substituent or p^{2}H value of the buffer. For the α-CD complexes in solution, the most probable positions of the phenyl rings determined here agree well with those in the solid state determined by X-ray crystallography[22–24]. Molecular models suggest that all of the phenols investigated here can penetrate up to the proposed position without any steric contact with the atoms inside the cavity of α-CD; further penetration would involve steric interaction of the hydrogens of the guest *meta* to the hydroxyl group with H-5 of α-CD. The six H-5 form a ring with a radius (~3.2 Å) smaller than that (3.6 Å) formed by the six H-3. Molecular models and the results of X-ray crystallography also indicate that, in the most probable position, the aromatic hydrogens of the guest phenols interact with H-3 and H-5 of α-CD. Thus, the most probable position of the guest phenols in the α-CD cavity reflects a balance between steric repulsion and the driving force for the complexation. Since the *p*-substituents of the phenols investigated do not interact severely with any part of α-CD at the probable position, the slight variations in these positions may reflect other than steric effects.

For the β-CD complexes, the ring formed by seven H-5 is large, and the phenolic compounds can penetrate more deeply into the cavity without severe steric interaction. The position determined to be the most probable for the centre of the phenyl ring in the β-CD cavity corresponds well with the centre of the hydrophobic cavity; there are no crystallographic data on β-CD inclusion-complexes. Several mechanisms have been proposed for the formation of CD inclusion-complexes[1–3,13,39–41], but it seems that hydrophobic interaction is the most probable.

At the probable position proposed for the phenolic compounds in the β-CD cavity, there is strong steric interaction between the aromatic protons *ortho* and *meta* to the phenolic hydroxyl-groups and H-3 and H-5. Molecular models indicate the restriction of the motion of the included phenolic compound imposed by this steric interaction to be larger in the β-CD cavity than in that of α-CD, as also found by ^{13}C spin–lattice relaxation-times[31,35].

There are also slight differences in the proposed positions of the respective phenolic compounds included in the β-CD cavity, which reflect the nature of the *p*-substituents.

Thus, the stability of the inclusion complexes of α-CD and β-CD with the phenols having *p*-substituents of moderate size depends on the guest, the CD, and the ionisation state of the CD hydroxyl-groups, but not significantly on the ionisation of the phenolic hydroxyl-groups. Also, the probable position of the centre of the phenyl rings of guests included in the CD cavity depends on the guest and the cavity size, and is independent of the ionisation of the guest phenolic hydroxyl-group. The dependence on the guests is relatively small and the position of the centre of the phenyl rings varies little. The guests in the β-CD complexes are more deeply inserted into the cavity than is the case for α-CD.

ACKNOWLEDGMENT

We thank the N.M.R. Appl. Lab., JEOL Ltd., for the measurements of 270-MHz, ^{1}H-n.m.r. spectra.

REFERENCES

1 R. J. Bergeron, *J. Chem. Educ.*, 54 (1977) 204–207.
2 M. L. Bender and M. Komiyama, *Reactivity and Structure Concepts in Organic Chemistry*, Vol. 6, *Cyclodextrin Chemistry*, Springer–Verlag, New York, 1978.
3 W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 19 (1980) 344–362.
4 I. Tabushi, *Acc. Chem. Res.*, 15 (1982) 66–72.
5 W. L. Hinze, *Sep. Purif. Methods*, 10 (1981) 159–237.
6 D. J. Wood, F. E. Hruska, and W. Saenger, *J. Am. Chem. Soc.*, 99 (1977) 1735–1740.
7 M. Komiyama and H. Hirai, *Chem. Lett.*, (1980) 1467–1470, 1471–1474; *Polymer J.*, 13 (1981) 171–173.
8 P. V. Demarco and A. L. Thakkar, *Chem. Commun.*, (1970) 2–4.
9 R. Bergeron and R. Rowan, *Bioorg. Chem.*, 5 (1976) 425–436.
10 J. P. Behr and J. M. Lehn, *J. Am. Chem. Soc.*, 98 (1976) 1743–1747.
11 Y. Inoue, Y. Katôno, and R. Chûjô, *Bull. Chem. Soc. Jpn.*, 52 (1979) 1692–1697.
12 K. Sensse and F. Cramer, *Chem. Ber.*, 102 (1969) 509–521.
13 R. I. Gelb, L. M. Schwartz, B. Cardelino, H. S. Fuhrman, R. F. Johnson, and D. A. Laufer, *J. Am. Chem. Soc.*, 103 (1981) 1750–1757.
14 J. Michon and A. Rassat, *J. Am. Chem. Soc.*, 101 (1979) 995–996.
15 M. Ohara, H. Hettler, D. Gauss, and F. Cramer, *Bioorg. Chem.*, 8 (1979) 211–217.
16 K. Harata, *Bioorg. Chem.*, 10 (1981) 255–265.
17 H. Shimizu, A. Kaito, and M. Hatano, *Bull. Chem. Soc. Jpn.*, 54 (1981) 513–519.
18 T. Yorozu, M. Hoshino, M. Imamura, and H. Shizuka, *J. Phys. Chem.*, 86 (1982) 4422–4426.
19 Y. Inoue, T. Okuda, and Y. Miyata, *J. Am. Chem. Soc.*, 103 (1981) 7393–7394.
20 A. Hybl, R. E. Rundle, and D. E. Williams, *J. Am. Chem. Soc.*, 87 (1965) 2779–2788.
21 P. C. Manor and W. Saenger, *J. Am. Chem. Soc.*, 96 (1974) 3630–3639.
22 K. Harata and H. Uedaira, *Nature (London)*, 253 (1975) 190–191.
23 W. Saenger, K. Beyer, and P. C. Manor, *Acta Crystallogr., Sect. B*, 32 (1976) 120–128.
24 K. Harata, *Bull. Chem. Soc. Jpn.*, 50 (1977) 1416–1424.
25 M. M. Harding, J. M. Maclennan, and R. M. Paton, *Nature (London)*, 274 (1978) 621–623.
26 K. Harata, H. Uedaira, and J. Tanaka, *Bull. Chem. Soc. Jpn.*, 51 (1978) 1627–1634.
27 M. Komiyama and H. Hirai, *Bull. Chem. Soc. Jpn.*, 54 (1981) 828–831.
28 R. L. VanEtten, G. A. Clowes, J. F. Sebastian, and M. L. Bender, *J. Am. Chem. Soc.*, 89 (1967) 3253–3262.
29 P. G. Stecher (Ed.), *The Merck Index*, 9th edn., Merck & Co., New Jersey, 1976.
30 P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 64 (1960) 188–190.
31 Y. Inoue and Y. Miyata, *Bull. Chem. Soc. Jpn.*, 54 (1981) 809–816.

32 R. J. Bergeron, M. A. Channing, G. J. Gibeily, and D. M. Pillor, *J. Am. Chem. Soc.*, 99 (1977) 5146–5151.

33 C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 29 (1958) 1012–1014.

34 R. J. Bergeron and M. A. Channing, *J. Am. Chem. Soc.*, 101 (1979) 2511–2516.

35 Y. Inoue, T. Okuda, and Y. Miyata, *Carbohydr. Res.*, 101 (1982) 187–195.

36 R. J. Bergeron, M. A. Channing, and K. A. McGovern, *J. Am. Chem. Soc.*, 100 (1978) 2878–2883.

37 R. I. Gelb, L. M. Schwartz, J. E. Markinac, and D. A. Laufer, *J. Am. Chem. Soc.*, 101 (1979) 1864–1868.

38 Y. Nakai, K. Yamamoto, K. Terada, and H. Horibe, *Chem. Pharm. Bull.*, 30 (1982) 1796–1802.

39 F. Cramer, W. Saenger, and H.-Ch Spatz, *J. Am. Chem. Soc.*, 89 (1967) 14–20.

40 W. Saenger, M. Noltemeyer, P. C. Manor, B. Hingerty, and B. Klar, *Bioorg. Chem.*, 5 (1976) 187–195.

41 I. Tabushi, Y. Kiyosuke, T. Sugimoto, and K. Yamamura, *J. Am. Chem. Soc.*, 100 (1978) 916–919.