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DETERMINATION OF THE HOST–GUEST GEOMETRY IN THE INCLUSION COMPLEXES OF CYCLOMALTO-OLIGOSACCHARIDES WITH *p*-NITROPHENOL IN SOLUTION

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ABSTRACT

The structures of the inclusion complexes of cyclomaltohexaose, cyclomaltoheptaose, and their methylated derivatives with *p*-nitrophenol in solution have been investigated. The position of the guest molecule in the complexes has been determined on the basis of ^{1}H-n.m.r. shift data, using the Johnson–Bovey theory. The results suggest that the stability of these inclusion complexes is not related simply to the depth of insertion of the guest molecule into the cavity of the host molecule and that various non-bonded interactions have to be considered.

INTRODUCTION

Cyclomalto-oligosaccharides (cyclodextrins, CDs) are cyclic oligosaccharides composed of six or more (1→4)-linked α-D-glucopyranosyl residues, which can accommodate various substances in their cavities to form inclusion complexes and can act as catalysts in chemical reactions[1–4]. These inclusion complexes have been investigated extensively both in the solid state and in solution. X-Ray crystallography has provided information on the structure of various inclusion complexes and helped to understand both the geometry of the host–guest complexes in the solid state and the intermolecular effects[5–7]. N.m.r. spectroscopy has been used to investigate the structure of the inclusion complexes in solution[8,9]. Measurements[10] of n.O.e.'s are useful for determining the orientation of the guest molecule in the cavity of CDs[8,9], and the effect of anisotropic shielding of the aromatic guest molecule has been used to probe the host–guest geometry[11,12]. The induced changes in chemical shifts of the ^{1}H resonances of the CD by the aromatic guest reflect the location of the corresponding protons with respect to the centre of the aromatic ring. The host–guest binding constants can be obtained by the n.m.r. "titration" method[12,13]. Determination of the host–guest geometry may provide an insight into

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the mechanisms of CD-catalysed reactions and the intermolecular interactions of the CD and the guest molecules.

We have investigated the structure of the inclusion complexes of cyclomaltohexaose (α-CD), cyclomaltoheptaose (β-CD), and their methylated derivatives (α- and β-MCD, respectively) with *p*-nitrophenol (pNP) in solution. The ^{1}H resonances of pNP are "titrated" with the individual CDs in order to obtain the host–guest binding constants. The changes in chemical shifts of the resonances of H-3 and H-5 of the CDs induced by pNP can be interpreted in terms of the spatial relationship between the H-3 and H-5 and the centre of the benzene ring of pNP based on the Johnson–Bovey theory[14]. Although a rigid conformation of the host molecule has been assumed in the previous calculations[11,12], an induced-fit type model has been constructed in which a conformational change of the macrocyclic ring of the CD on complexation is considered. Since the structures of the macrocyclic rings of MCDs appear to be distorted in solution[15], such an induced-fit type model is appropriate for these compounds. We now report on measurements carried out at pH 3 and 10 in order to investigate the effect of the ionisation state of pNP on the stability and the geometry of the inclusion complexes.

EXPERIMENTAL

Materials. — α-CD and β-CD (Nihon Shokuhin Kako Co. Ltd.) and α-MCD (Toshin Chemical Co.) were recrystallised and then dried at 105° under vacuum for several hours before use. α-MCD was obtained by methylation of α-CD, using the Kuhn–Trischmann method[16,17], and its purity was established by the n.m.r. spectrum (**A** of Fig. 1). pNP (Tokyo Kasei Kogyo Co.) was recrystallised three times from chloroform as light-yellow needles, m.p. ~236°. The pH values were determined by using a Toko TP-101 pH-meter equipped with a micro combination-electrode CE103, and DCl or NaOD was used to adjust the pD.

^{1}H-N.m.r. measurements. — 500-MHz ^{1}H-n.m.r. spectra were recorded on solutions in D_2O at 27° with a JEOL GX-500 FT spectrometer, using 64–128 transients with 32K data points over a spectral width of 5000 Hz. The spectra were apodised with an exponential window function which introduced 0.3-Hz line-broadening. Chemical shifts are given in p.p.m. downfield from the signal for Me_4Si.

Dissociation constants (K_d). — The stoichiometry and the K_d values of the reaction between CD derivatives and pNP have been determined using u.v. and ^{1}H-n.m.r. titrations. Since the results agreed within experimental error, the ^{1}H-n.m.r. method was used.

RESULTS

The ^{1}H-n.m.r. spectra (500 MHz) of α-MCD in the absence and presence of pNP at 27° and pD 10 are illustrated in Fig. 1. The assignments were based on

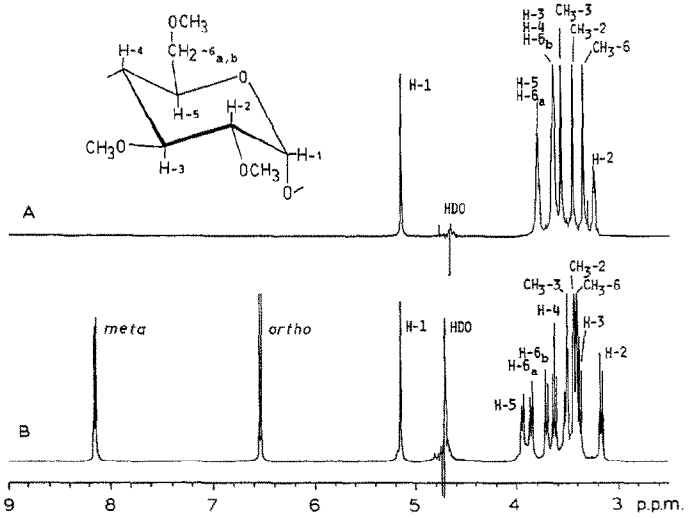

Fig. 1. 500-MHz ^{1}H-n.m.r. spectra of **A**, 0.1M α-MCD; and **B**, 0.03M α-MCD and 0.1M pNP in D_2O (pD 10) at 27°.

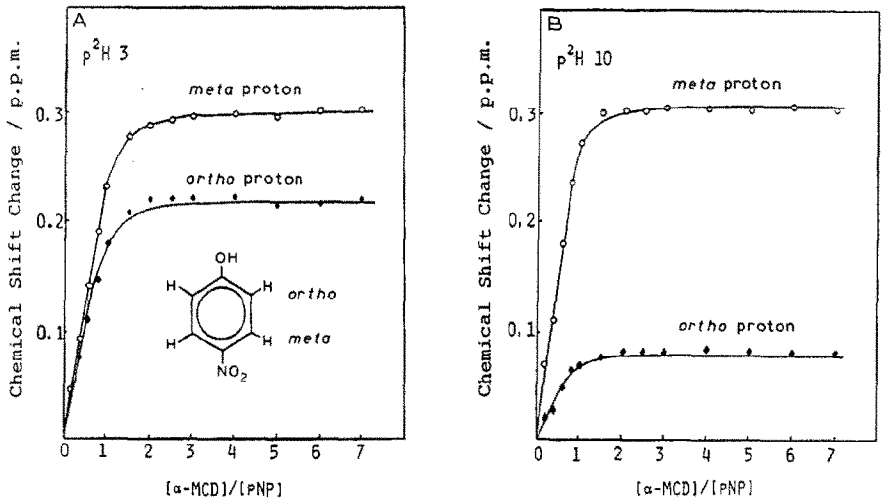

Fig. 2. Plots of the changes in chemical shift of the resonances of the *meta* and *ortho* protons of pNP as a function of the molar ratio ([α-MCD]/[pNP]) at **A** pD 3 and **B** pD 10.

2D-n.m.r. experiments (results not shown). Large shifts in the resonances of H-3 and H-5 induced by the addition of pNP indicate complexation and the effect of the magnetic field created by the benzene ring current of pNP. On the other hand, the downfield shift of the resonances of the *meta*- and *ortho*-protons of pNP allows determination of the stoichiometry and the dissociation constant. The results obtained from the titration of pNP with α-MCD at pD 3 and 10 are given in Fig. 2.

TABLE I

DISSOCIATION CONSTANTS (K_d)[a] OF THE INCLUSION COMPLEXES OF CDs AND MCDs WITH pNP DETERMINED BY ^{1}H-N.M.R. AND U.V. TITRATIONS

	^{1}H-N.m.r.		*U.v.*	
	pD 3	*pD 10*	*pD 3*	*pD 10*
α-CD	5.8×10^{-3}	6.1×10^{-4}	4.9×10^{-3}	2.9×10^{-4}
α-MCD	5.5×10^{-4}	8.0×10^{-5}	7.5×10^{-4}	6.8×10^{-5}
β-CD	[b]	1.5×10^{-3}	5.4×10^{-3}	1.3×10^{-3}
β-MCD	9.9×10^{-3}	6.9×10^{-3}	7.5×10^{-3}	3.2×10^{-3}

[a]Dissociation constants are given in M. [b]Not determined due to the low solubility of β-CD.

The shifts in the resonances of the *meta*- and *ortho*-protons are attributed largely to solvent effects. The data in Fig. 2 indicate a 1:1 complex, and similar results were obtained for other CDs except β-MCD for which the downfield shift of the *ortho*-proton resonances of pNP was larger than that of the *meta*-proton. The orientation of the pNP molecule in the cavity of CD in solution inferred from the magnitude of the changes in the chemical shifts of the resonances of the *meta*- and *ortho*-protons indicates that the pNP is incorporated into the cavity of β-MCD from the phenolic hydroxyl group.

The dissociation constants (K_d) determined by the ^{1}H-n.m.r. and u.v. absorption methods are given in Table I. Although the concentration of the sample is at least three orders of magnitude different between the two methods, the K_d values are similar, indicating that the interaction is independent of the concentration.

The Johnson–Bovey theory predicts the magnitude of the shielding effect induced by the ring-current of the benzene on a proton if the location of the proton with respect to the benzene ring is known[14]. Hence, the spatial relationship between the protons of the CD and the benzene ring of the guest molecule (the host–guest geometry) can be determined from the ^{1}H-n.m.r. data[11].

The following assumptions are made. (*1*) In the inclusion complexes, the C_2 axis of symmetry of the pNP molecule is aligned with the axis of symmetry of the host molecule. (*2*) The effect of substituents on the π-electron density of the benzene ring is neglected. (*3*) Magnetic anisotropy effects arising from the substituents of pNP on the proton resonances of the CD are neglected. Therefore, the direction of insertion of pNP into the CD cavity cannot be predicted.

The procedure for determining the position of the pNP molecule then involves three steps. (*1*) The changes ($\Delta\delta$) in chemical shifts of the resonances of H-3 and H-5 of the CD induced by the addition of pNP are observed and, using the K_d values given in Table I, $\Delta\delta$ values are corrected to obtain the limiting values ($\Delta\delta_0$), *i.e.*, the difference between the free and fully complexed states (see Table II). (*2*) The magnitudes of the anisotropic shielding effects arising from the aromatic ring on the resonances of H-3 and H-5 are evaluated as a function of the depth of inser-

TABLE II

OBSERVED ($\Delta\delta$) AND LIMITING ($\Delta\delta_0$) CHANGES IN THE CHEMICAL SHIFT OF THE RESONANCES OF H-3 AND H-5 OF CDs INDUCED BY COMPLEXATION WITH pNP

	pD	$\Delta\delta$ *(p.p.m.)*[a]		$\Delta\delta_0$ *(p.p.m.)*[b]	
		H-3	*H-5*	*H-3*	*H-5*
α-CD	3	−0.22	−0.03	−0.37	−0.05
	10	−0.25	0.00	−0.27	0.00
α-MCD	3	−0.39	0.02	−0.41	0.02
	10	−0.31	0.11	−0.31	0.11
β-CD	10	−0.12	−0.18	−0.14	−0.21
β-MCD	3	−0.14	−0.04	−0.29	−0.08
	10	−0.14	−0.06	−0.25	−0.11

[a]Obtained for the solution ([Guest]/[Host] = 0.01M/0.002M); negative values indicate upfield shifts. [b]Calculated from the $\Delta\delta$ values, using the dissociation constants given in Table I.

tion of pNP into the cavity of the CD on the basis of the Johnson–Bovey theory. Based on models (see below), the changes in chemical shift of the resonances of H-3 and H-5 are calculated as the weighted average of the changes in chemical shifts for six (α-CD and α-MCD) or seven (β-CD and β-MCD) corresponding protons. (*3*) The position of pNP in the cavity of the CD is determined when the difference between the $\Delta\delta_0$ value and the calculated change in chemical shift is a minimum for H-3 and H-5.

The Johnson–Bovey theory is summarised in the Appendix. Two parameters, ρ and z, are affected by the position of pNP with respect to the CD. The distance between the centre of the benzene ring of pNP and the plane comprised of the H-3 atoms of the CD is designated as d and is positive when the centre of the benzene ring is on the side of H-5 with respect to this plane. The models assumed are shown in Fig. 3 and a simple mode of conformational change on the macrocyclic ring structure of the CD molecule on complexation with pNP is considered. The Johnson–Bovey curves calculated for H-3 and H-5 of the complexes of α-CD and α-MCD, using the models **A** and **B**, are given in Fig. 4; the horizontal axis indicates the distance between the centre of the benzene ring of pNP and the plane comprised of the H-3 atoms of the CDs, and the vertical axis the change in chemical shift of the resonances of H-3 or H-5. The Johnson–Bovey curve for the H-3 resonance is symmetrical with respect to the vertical line through $d = 0$ and the curve for the H-5 resonance is a single-valued function in the region, $-1 < d < 2.5$. Those curves are sensitive to d, and therefore the position of the benzene ring of pNP with respect to H-3 and H-5 of CD can be determined graphically using the $\Delta\delta_0$ values for the resonances of H-3 and H-5. For example, for the α-CD–pNP complex at pD 10, the $\Delta\delta_0$ values of −0.27 and 0.00 p.p.m. for H-3 and H-5, respectively, yield a d value of 0.8 ±0.1 Å with $X = 0.5$ Å, using the Johnson–Bovey curves in Fig. 4A. This result is consistent with the structure deduced from the n.O.e. data[8,9] and also

agrees with the X-ray results[5]. The d values of the other inclusion complexes with α-CD and α-MCD have been determined similarly. Likewise, C in Fig. 3 is assumed for the inclusion complexes of β-CD and β-MCD, and the Johnson–Bovey curves are given in Fig. 5. The d values are summarised in Table III. For the complexes of α-CD and α-MCD, the d values obtained from the two different models agree. Although the d values for α-CD and α-MCD are similar, the hydrophobic space inside the cavity should be greater in α-MCD than in α-CD because of the methoxyl groups (see Fig. 6) and, therefore, the stabilisation energy arising from the hydrophobic interaction will be greater for the α-MCD–pNP complex than for the α-CD–pNP complex, as reflected in the K_d values.

DISCUSSION

Both the ^{1}H-n.m.r. and u.v. methods reveal a 1:1 complex between pNP and the various CDs used in this study, and the K_d values are summarised in Table I. The stability of the inclusion complexes is greater in basic solution than in acidic solution. Since there are no ionisable hydroxyl groups in the MCDs, the difference in the stability of inclusion complexes reflects the different effects of ionisation of pNP. pNP has a pK_a of 7.2 and is fully ionised at pH 10, and the negative charge is delocalised over the benzene ring. Electrostatic effects between pNP and the CDs may be important for the stabilisation of the inclusion complexes.

As shown in Fig. 2, the resonance of the *meta*-proton of pNP is usually shifted more than that of the *ortho*-proton on addition of CDs, except for β-MCD. Since the titration behaviour of those two resonances for the α-MCD system is similar to

TABLE III

POSITION[a] OF pNP IN CDs DETERMINED FROM JOHNSON–BOVEY CURVES

	α-CD		*α-MCD*	
	pD 3	*pD 10*	*pD 3*	*pD 10*
MODEL A	0.7 ±0.2 ($X = 0.8$)[b]	0.8 ±0.1 ($X = 0.5$)	0.8 ±0.3 ($X = 1.0$)	0.6 ±0.1 ($X = 0.6$)
MODEL B	0.9 ±0.4 (n.d.)	0.9 ±0.4 ($Y = 0.5$)	0.6 ±0.2 ($Y = 0.2$)	0.6 ±0.3 (n.d.)
	β-CD		*β-MCD*	
	pD 10		*pD 3*	*pD 10*
MODEL C	1.3 ±0.1 ($\theta = 5$)		0.7 ±0.2 ($\theta = 12$)	0.8 ±0.2 ($\theta = 10$)

[a]In Å; distance between the centre of the benzene ring of pNP and the plane comprised of the H-3 atoms. Positive values mean that the centre of the benzene ring is located on the side of H-5 with respect to the plane of the H-3 atoms. [b]Numbers in parentheses indicate the values of the adjusting parameters defined in Fig. 3. X, Y, and θ are given in Å, Å and degrees, respectively; n.d. not determined.

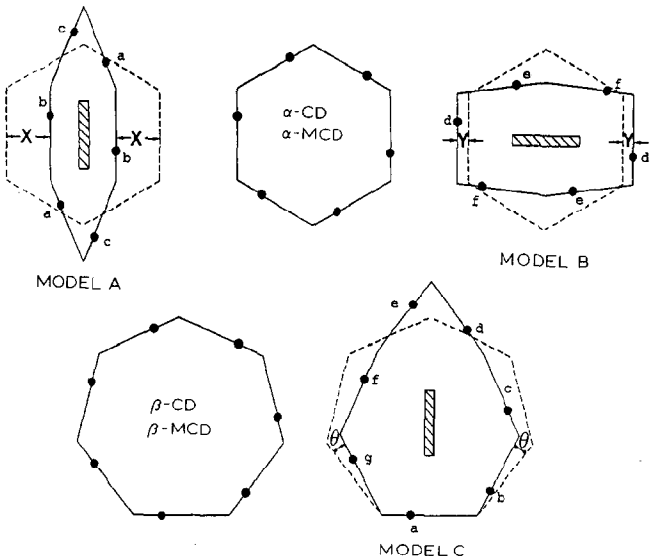

Fig. 3. Models used for the calculations: **A** and **B** for α-CD and α-MCD, and **C** for β-CD and β-MCD. The positions of H-3 (or H-5) are indicated by ● and the rectangular hatched area represents the plane of the benzene ring of pNP which is parallel (**A**) or perpendicular (**B**) to one pair of opposite glucopyranose residues. Displacements of X and Y in models **A** and **B**, respectively, are considered, and the magnetic anisotropy effects are calculated for the individual protons and averaged. In model **C**, the plane of the benzene ring is perpendicular to one of the glucopyranose residues and the distortion of the angle, θ, on the macrocyclic ring structure on complexation is considered. See Appendix for the assignment of a–c in model **A**, d–f in model **B**, and a–g in model **C**.

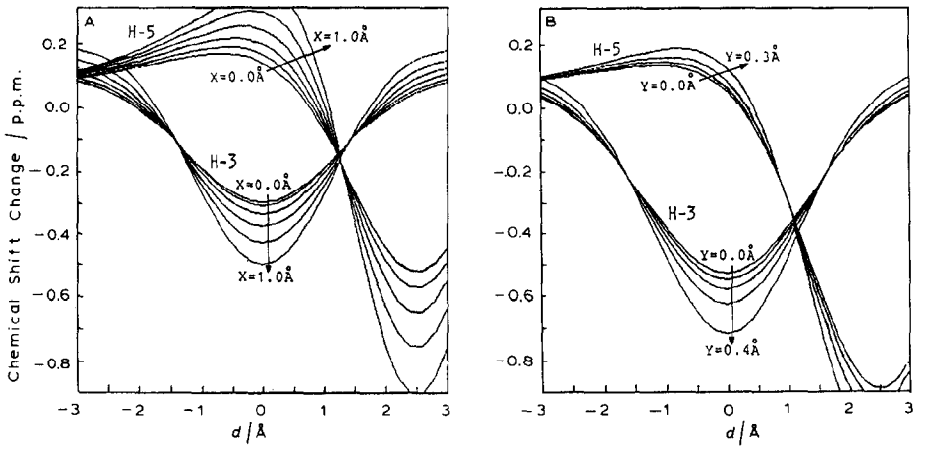

Fig. 4. Johnson–Bovey curves calculated for the inclusion complexes of α-CD and α-MCD, using models **A** and **B**.

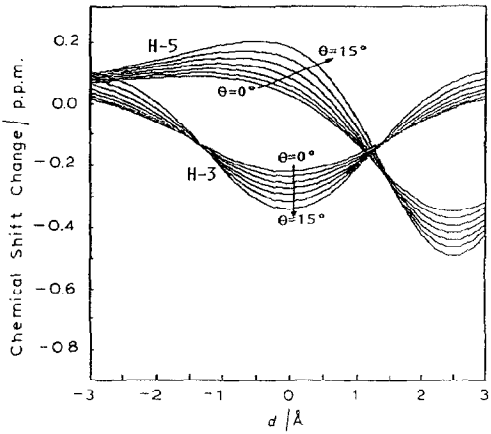

Fig. 5. Johnson–Bovey curves calculated for the inclusion complexes of β-CD and β-MCD, using model **C**.

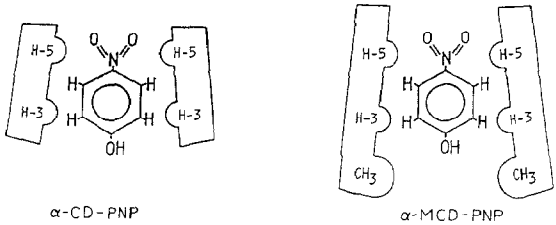

Fig. 6. Calculated host–guest geometry of **A** α-CD–pNP and **B** α-MCD–pNP complexes. In **B**, the orientation of pNP is that deduced from the ^{1}H-n.m.r. shift data[18]. The α-CD–pNP structure agrees with its X-ray result[5].

that of α-CD, the orientation of pNP in the cavities was considered to be the same[18], although the X-ray crystal structure indicated the reverse orientation[6]. If the relative magnitude of the changes in chemical shifts for the resonances of the *meta*- and *ortho*-proton reflects the orientation of the pNP molecule in the cavity of CD in solution, the larger change in chemical shift of the *ortho*-proton in the β-MCD system indicates that the orientation of pNP in β-MCD is opposite to that in α-MCD.

According to the K_d values shown in Table I, the limiting chemical shift changes ($\Delta\delta_0$) for H-3 and H-5 are calculated from the observed changes ($\Delta\delta$) and are listed in Table II. The position of the guest molecule in the cavity of CD was based on the $\Delta\delta_0$ values. On the assumptions given above, the effect of the benzene ring of pNP on the chemical shifts of the resonances of H-3 and H-5 of the CDs can be calculated using the Johnson–Bovey theory. Although a similar approach has been applied to other CD inclusion complexes, the cavity of CD was considered to be rigid in the previous calculations[11]. Such a model does not account for our results and therefore the induced-fit type complexation models shown in Fig. 3 were con-

structed; in these, a conformational change on the macrocyclic ring of the host molecule on the complexation with pNP is taken into account. Models **A** and **B** are considered for α-CD and α-MCD, and the parameters, X and Y, are changed systematically in the calculation. Model **C** is assumed for β-CD and β-MCD. ^{13}C-N.m.r. relaxation studies suggest that the pNP molecule rotates rapidly about its C_2 axis of symmetry inside the cavity of the CDs in solution[19,20]. A random fluctuation of the macrocyclic conformation of the CDs is supposed to take place in solution, but this process is not taken into consideration in the models. The d values determined by the present method, together with the adjusted values of the parameters X and Y (for α-CD and α-MCD) and θ (for β-CD and β-MCD) are summarised in Table III. The results for α-CD and β-CD confirm that pNP is more deeply incorporated into β-CD than into α-CD, although the inclusion complex of α-CD is more stable than that of β-CD as reflected in the K_d values. Since the diameter of the cavity of β-CD is ~1 Å larger than that of α-CD, van der Waals interaction may be favorable for the inclusion complexation of α-CD with pNP. Therefore, the stability of the inclusion complexes is not related simply to the depth of insertion of pNP into the cavity of CD. The intermolecular interaction energy that controls complexation should account for the stability of the inclusion complexes. The host–guest geometry determined for α-CD–pNP and α-MCD–pNP complexes are illustrated in Fig. 6. Because of the methoxyl groups, pNP is completely incorporated into the hydrophobic cavity of α-MCD with a d value of 0.6 Å, and the difference in the hydrophobic interaction energy between the complexes of α-CD and α-MCD may be responsible in part for the difference in the stability between two complexes in solution. Although a conformational change of the macrocyclic structure of CD on complexation could not be determined using the models presented here, it is suggested that some conformational change is induced because the changes in chemical shift of the resonances of H-3 and H-5 of the CDs due to the complexation with pNP are predicted more reasonably by the induced-fit models.

ACKNOWLEDGMENT

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APPENDIX

Johnson–Bovey Theory

$$\Delta\delta = \frac{-ne^2}{6\pi mc^2 R} \cdot \frac{1}{[(1+\rho)^2 + z^2]^{1/2}} \cdot \left[K + \frac{1-\rho^2-z^2}{(1-\rho)^2+z^2} \cdot E \right] \times 10^6$$

$$K = \int_0^{\pi/2} \frac{d\theta}{\sqrt{1-k^2\sin^2\theta}} \qquad \text{(Complete elliptic integral of the first kind)}$$

$$= 0.5\pi \left[1 + \left(\frac{1}{2}\right)^2 k^2 + \left(\frac{1\cdot 3}{2\cdot 4}\right)^2 k^4 + \cdots + \left\{\frac{(2r-1)!!}{(2r)!!}\right\}^2 k^{2r} + \cdots \right]$$

$$E = \int_0^{\pi/2} \sqrt{1-k^2\sin^2\theta}\, d\theta \qquad \text{(Complete elliptic integral of the second kind)}$$

$$= 0.5\pi \left[1 - \left(\frac{1}{2}\right)^2 k^2 - \left(\frac{1\cdot 3}{2\cdot 4}\right)^2 \frac{k^4}{3} - \cdots - \left\{\frac{(2r-1)!!}{(2r)!!}\right\}^2 \frac{k^{2r}}{2r-1} - \cdots \right]$$

where $(2r-1)!! = (2r-1)\cdot(2r-3)\cdots 3\cdot 1$
$(2r)!! = (2r)\cdot(2r-2)\cdots 4\cdot 2$

$$k^2 = \frac{4\rho}{(1+\rho)^2+z^2}$$

$\Delta\delta$ (p.p.m.) = Change in the chemical shift of the resonance of H-3 or H-5 induced by the benzene ring current effect of pNP.

ρ = Distance between the centre of the benzene ring and the point at which the H-3 or H-5 is projected perpendicularly on to the plane of the benzene ring, divided by C–C bond length in benzene.

d (Å) = Distance between the centre of the benzene ring and the plane comprised of H-3; d is positive when the centre of the benzene ring is on the side of H-5 relative to this plane.

z = Distance between the plane of the benzene ring and the H-3 or H-5, divided by C–C bond length in benzene.

n = 6 (Number of π-electrons on benzene ring);
e = 4.81×10^{-10} (esu) (charge of electron);
m = 9.11×10^{-28} (g) (mass of electron);
c = 3.00×10^{10} (cm.s^{-1}) (speed of light);
R = 1.39×10^{-8} (cm) (C–C bond length in benzene).

Parameters of Johnson–Bovey equation

For α-CD, $r = 3.5$ for H-3, $r = 2.9$ for H-5.
For α-MCD, $r = 3.6$ for H-3, $r = 2.8$ for H-5.

$$z\,(a) = (\sqrt{3}r - 2X)/3$$
$$z\,(b) = (\sqrt{3}r - 2X)/2$$
$$z\,(c) = (\sqrt{3}r - 2X)/6$$
$$z\,(d) = r/6$$
$$z\,(e) = \{3r + 2[r^2 - 4X(X - \sqrt{3}r)]^{1/2}\}/6$$
$$z\,(f) = \{3r - [r^2 - 4X(X - \sqrt{3}r)]^{1/2}\}/6$$

$$\rho\,(a) = \{D^2 + [\{3r + [r^2 - 4X(X - \sqrt{3}r)]^{1/2}\}/6]^2\}^{1/2}$$
$$\rho\,(b) = [D^2 + (r/6)^2]^{1/2}$$
$$\rho\,(c) = \{D^2 + [\{3r + 2[r^2 - 4X(X - \sqrt{3}r)]^{1/2}\}/6]^2\}^{1/2}$$
$$\rho\,(d) = \{D^2 + [\sqrt{3}r - 2X)/3]^2\}^{1/2}$$
$$\rho\,(e) = \{D^2[\sqrt{3}r - 2X)/2]^2\}^{1/2}$$
$$\rho\,(f) - \{D^2 + [(\sqrt{3}r - 2X)/6]^2\}^{1/2}$$

where a–f, shown in parentheses of z and ρ, correspond to H-3 or H-5 in models A or B as shown in Fig. 3.

$D^2 = d^2$ for H-3
$D^2 = (2.5 - d)^2$ for H-5

For β-CD, $r = 4.1$ for H-3, $r = 3.4$ for H-5.
For β-MCD, $r = 4.2$ for H-3, $r = 3.3$ for H-5.

$$z\,(a) = SA/3$$
$$z\,(b) = (SA + 2SB)/3$$
$$z\,(c) = (SB + 2SC)/3$$
$$z\,(d) = SC/3$$
$$z\,(e) = (2SA + SB)/3$$
$$z\,(f) = (2SB + SC)/3$$
$$z\,(g) = 2SC/3$$

$$\rho\,(a) = [D^2 + (TA/3)^2]^{1/2}$$
$$\rho\,(b) = \{D^2 + [(TA + 2TB)/3]^2\}^{1/2}$$
$$\rho\,(c) = \{D^2 + [(TB + 2TC)/3]^2\}^{1/2}$$
$$\rho\,(d) = \{D^2 + [(TC + 2TD)/3]^2\}^{1/2}$$
$$\rho\,(e) = \{D^2 + [(2TA + TB)/3]^2\}^{1/2}$$
$$\rho\,(f) = \{D^2 + [(2TB + TC)/3]^2\}^{1/2}$$
$$\rho\,(g) = \{D^2 + [(2TC + TD)/3]^2\}^{1/2}$$

where a–g, shown in parentheses of z and ρ, correspond to H-3 or H-5 in model C as shown in Fig. 3.

$D^2 = d^2$ for H-3
$D^2 = (2.5 - d)^2$ for H-5

$SA = r\sin(360/14)$
$SB = SA + 2r\sin(360/14)*\cos(90 + 360/7 + \theta)$
$SC = SB - 2r\sin(360/14)*\cos(180 - 720/7 - \theta)$
$TA = -r\cos(360/14)$
$TB = -r\sin(90 + 180/7) - 2\sin(180/7)*\cos(90 - 360/7 - \theta)$
$TC = TB + 2r\sin(360/14)*\cos(720/7 - 90 + \theta)$
$TD = TB + \{[2r\sin(360/14)]^2 + SC^2\}^{1/2}$

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