

GEOMETRY OF α -CYCLODEXTRIN INCLUSION-COMPLEXES WITH SOME SUBSTITUTED BENZENES DEDUCED FROM C-13 NMR CHEMICAL SHIFTS*

Y. Inoue , H. Hoshi , M. Sakurai , and R. Chûjô
Department of Polymer Chemistry
Tokyo Institute of Technology
O-okayama 2-chome , Meguro-ku , Tokyo 152
Japan

ABSTRACT. The geometries of inclusion complexes of α -cyclodextrin(α -CD) with guests , benzoic acid , p-hydroxy benzoic acid , and p-nitrophenol in aqueous solution have been determined by comparing the complexation induced C-13 shifts of guest molecules with quantum chemical predictions. In the calculations , the non-polar environmental effect produced by the α -CD cavity on the C-13 shifts of included guest molecule has been formulated by the so-called solvent effect theory. The geometries of the complexes predicted theoretically were consistent with those in aqueous solution determined by H-1 NMR and those in the solid by the X-ray method.

1. INTRODUCTION

High resolution C-13 NMR spectroscopy is one of the most useful methods in the analysis of the structure and molecular dynamics of cyclodextrin inclusion-complexes both in aqueous solution[1,2] and in the solid state[3]. Earlier C-13 NMR studies of α -CD inclusion complexes with benzoic acid(BA), p-nitrophenol(PNP), and p-nitrophenolate in aqueous solution have shown that the included lead(head; see Fig.1A) carbons show high-field shifts compared to low-field shifts of corresponding para(tail;Fig.1A) carbons[4,5], as shown in the last column of Table II. Similar distinctive patterns of C-13 displacements have been also observed for p-hydroxybenzoic acid(PHBA) and it has been concluded that the carboxyl group of PHBA is directed into the α -CD cavity[4]. A variety of substituted benzenes are known to show quite similar C-13 high(head) and low(tail) field shifts, irrespective of the kinds of substituents if their size are matched to the α -CD cavity[4,5]. These characteristic C-13 displacements induced by complexation with α -CD may be useful in inferring the extent of the host-guest complexation and the orientation of the guest in the α -CD cavity, if the origin of these C-13 displacements is accounted for.

* Details containing a more complete methodology and complete data will be published elsewhere.

In general, there are several kinds of non-bonded interactions, which may influence the C-13 chemical shifts. Among them, the electrical environmental effects are expected to be the major contribution to the α -CD complexation-induced C-13 displacements of head and tail carbons of the guest compounds, as these shifts are induced by moving the guest molecule from the free state, surrounded by polar water molecules, to the relatively non-polar α -CD cavity. This expectation is supported by the observations of the different trends of C-13 shift displacements in the high-resolution solid state C-13 NMR spectra of corresponding α -CD inclusion complexes[3]. In the solid-state, the α -CD complexation induced shifts are caused by transference of the guest molecule from the free state, surrounded by the same molecules, to the CD cavity.

In the case of NMR shielding, such environmental effects could be treated as solvent effects[6]. We reports here the preliminary determination of structures of α -CD inclusion-complexes with some substituted benzenes in aqueous solution by comparing the α -CD complexation induced-shifts of head and tail carbons of guests with predictions calculated by the application of a quantum-chemical model of solvent effects on C-13 shielding. BA, PHBA, and PNP were chosen as guests, since α -CD complexation-induced C-13 shifts in aqueous solution were available[4]. In solution, these compounds form 1:1 inclusion complexes with α -CD. The molecular structures in the crystalline state and in solution of the complexes between α -CD and PNP and PHBA have been characterized by X-ray diffraction[7] and H-1 NMR[5], respectively.

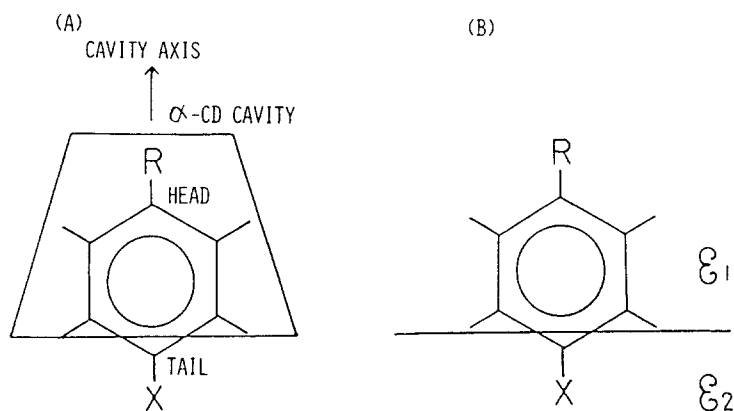


Figure 1. (A) Geometry of α -CD inclusion-complexes with benzene derivatives. (B) Double-layer model. The benzene derivative is situated on the borderline dividing the surroundings into two layers of dielectric constants, ϵ_1 and ϵ_2 .

2. METHODS

To calculate C-13 chemical shifts, we used the Karplus and Pople's average excitation energy method using CNDO/2 parameters[8], since this method was found to give good linearity between the calculated and observed C-13 shifts, as shown in Fig.2.

Molecular orbital calculations were carried out on a HITAC-M280 computer at the Information Processing Center of Tokyo Institute of Technology. The calculations of CNDO/2 containing the effects of solvent and of C-13 shifts were made using the program originally written by Professor Ando and modified by one of authors (H. H.) to include the effect of heterogeneous solvent effects. In the calculations, the geometry of these guest compounds were determined from the standard parameters[8] and the relative orientations of the substituents were taken to be the same as those in the solid-state α -CD inclusion-complexes determined by the X-ray method[7]. As the method of C-13 shift calculation, we also examined two other procedures, i.e., sum-over-state method and finite perturbation method both using INDO parameters, but we could not find any correlation between the calculated and observed C-13 shifts.

C-13 NMR spectra of BA, PHBA, and PNP in a series of solvents were recorded at 30°C on a JEOL JNM PS-100 NMR spectrometer equipped with a PFT-100 Fourier transform system at 25.14 MHz.

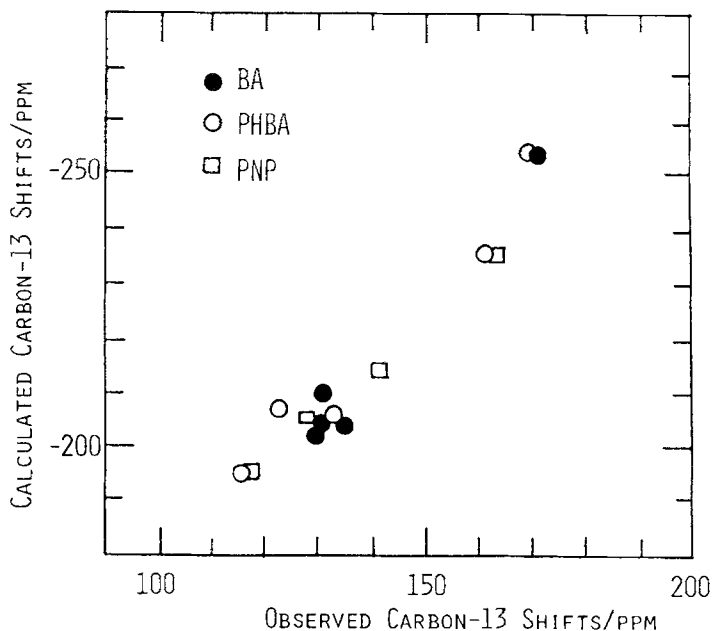


Figure 2. Correlation between calculated(reference; isolated C-13 nucleus in vacuum) and observed C-13 shifts(reference; external TMS in aqueous solution. Ref.4).

3. APPLICABILITY OF THE MODEL OF SOLVENT EFFECT ON C-13 SHIFTS

As the model of solvent effect on C-13 chemical shifts, we used one developed by Ando et al.[6] based on a Klopman's "Solvaton" theory[9]. This model has been successfully applied to interpret the dielectric solvent effect on C-13 chemical shifts of many organic compounds. According to this model, the interaction of solute with solvent molecules is incorporated into semi-empirical MO calculations by an assumption of a virtual particle called a solvaton.

To examine the applicability and the limits of the CNDO/2-solvaton combined method, the C-13 chemical shifts were calculated for PHBA as a function of dielectric constant(ϵ), and the results were compared with those observed in several solvents of a wide range of ϵ values as listed in Table I. In the calculations, effective van der Waals radii ($\times 10^{-10}\text{m}$) for hydrogen, carbon, nitrogen, and oxygen were assumed to be 1.20, 1.59, 1.50, and 1.40, respectively. In fig.3, the calculated and observed C-13 shifts are plotted against the factor $(\epsilon-1)/2\epsilon$. The linear dependence on $(\epsilon-1)/2\epsilon$ is found for both observed and calculated C-13 shifts. The same linear dependences were also

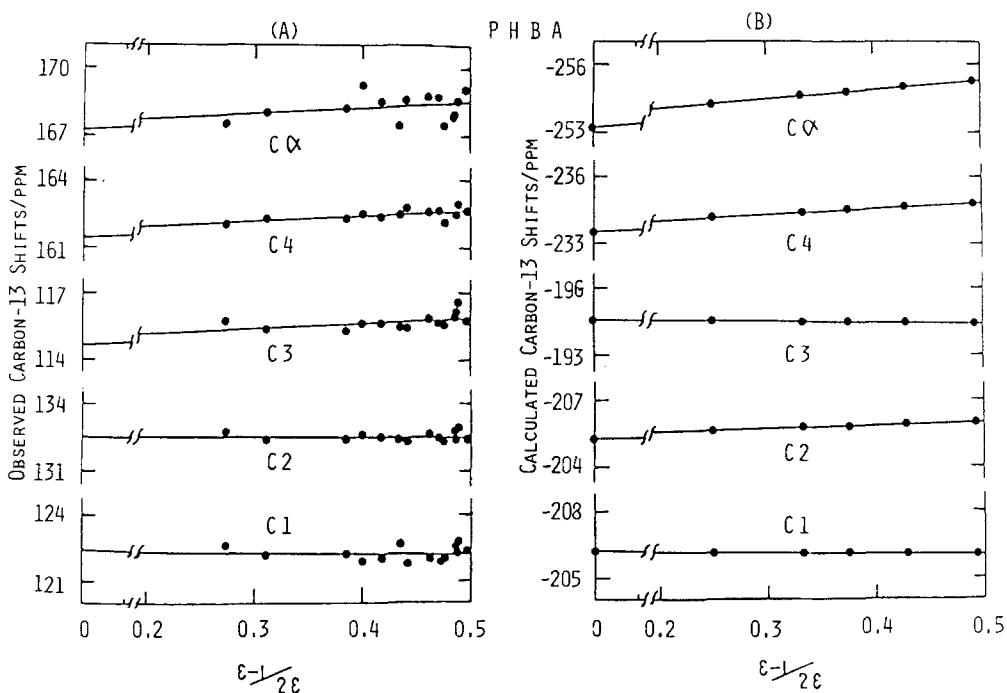


Figure 3. Dependence of (A) observed and (B) calculated C-13 shifts of PHBA on dielectric constants of solvents.

TABLE I. Solvents and their dielectric constants

Solvents	Dielectric Constant*
Ethyl oxalate	1.80
Dioxane	2.209
Dimethoxymethane	2.645
Ethyl carbonate	2.820
Ethyl ether	4.335
Butyl acetate	5.01
Ethyl acetate	6.02
Tetrahydrofuran	7.58
Methylformate	8.5
4-Methyl-2-pentanone	13.11
3-Pentanone	17.00
Acetone	20.70
N,N-Dimethylformamide	36.71
γ -Butyrolactone	39
Dimethyl sulfoxide	46.82
N-Methylformamide	182.4

* J. A. Riddick and W. B. Bunger "Techniques of Chemistry , vol.II, Organic Solvents, 3rd Ed." Wiley-Interscience, New York, 1970.

observed for BA and PNP(not shown). Thus it was confirmed that the gross trends of the solvent dependent C-13 shifts of BA, PHBA, and PNP are reproducible by the MO calculations.

It is well known that by forming inclusion complexes in aqueous solution with α -CD some compounds such as p-t-butylphenol show UV spectral changes almost identical to that observed when the compounds are dissolved in dioxane[10]. These results lead to a possibility that the C-13 shift displacements of the guest induced by complexation with α -CD may be explainable as shift changes when the guest is transferred from water($\epsilon=80$) to the hydrophobic environment of dioxane ($\epsilon = 2$). Therefore, the chemical shift differences $\Delta\delta = \delta_2 - \delta_{80}$ were calculated, where δ_2 and δ_{80} were chemical shifts in media of ϵ values 2 and 80, respectively. The results are shown in the first column of Table II as "the continuum model", since the CD cavity and the aqueous media were assumed in the calculations to be continua of $\epsilon = 2$ and 80, respectively. The α -CD induced shifts for BA carboxyl and Cl, PHBA carboxyl, and PNP C4 are reproduced qualitatively by the continuum solvent effect model, while those for corresponding para carbons(BA C4, PHBA C4, and PNP Cl) are not. The main reason for the failure of the continuum solvent effect model in explaining the α -CD complexation-induced shifts for the latter carbons may be due to the disregard of the actual structure of the inclusion complexes. The H-1 NMR study of α -CD inclusion complexes with p-substituted phenols in aqueous solution has led to their geometries, where a part of the included guest molecules is exposed to the aqueous medium[5].

Therefore in the following section, the C-13 shifts were calculated by the solvaton theory based on a more realistic "double-layer" model.

The trends of the α -CD complexation-induced shifts for the protonated carbons, i.e., C2 and C3, of each guest compound, are also not always reproducible by the continuum solvent effect model. Since the hydrogen atoms bonded to these carbons can contact with α -CD's H-3 and H-5 located inside the cavity in the complexed state, the steric shielding effect must also be considered for the explanation of the C-13 shifts of these carbons.

4. GEOMETRY OF α -CD INCLUSION-COMPLEXES BASED ON C-13 SHIFTS

In order to take into account the heterogeneous nature of the surroundings around the guest molecule in the α -CD inclusion-complex, a more realistic solvaton model was constructed. It was assumed that the α -CD cavity has the environmental(solvent) effect of dielectric constant ϵ_1 on the included part of the guest molecule, while the other part of the guest is exposed to the aqueous layer of dielectric constant ϵ_2 , as shown in Fig.1B. We called this "the double-layer model". It was further assumed that only two orientations are possible for the guest molecules on complexation, i.e., the substituent R or X is in the lead(Fig.1B). The latter assumption is reasonable according to experimental results[4,5].

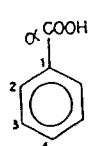
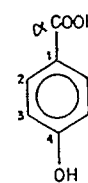
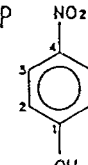
The C-13 shifts displacements were calculated as the function of the position of the borderline dividing the two layers. In the calculations, the accurate position of the borderline is unimportant, but what is important is which atom is included in the layer ϵ_1 and which remains in another layer of ϵ_2 . A series of calculations were made by shifting the borderline at different positions and also by reversing the orientation of the guest relative to the α -CD cavity.

By comparing the calculated and observed C-13 displacements, we tried to determine the geometry of the inclusion complexes. Here, the C-13 displacements of only the head and tail carbons are taken into account, because those of the other carbons may contain the contribution from the steric shielding effects, which were not taken into account in our calculations. For three host-guest systems, the observed characteristic C-13 displacements, i.e., the high-field shifts of the head carbons and the low-field shifts of the tail carbons, are reproduced only when the borderline in each system is on the shaded region as shown in Fig.4, here the orientation of the guest molecule is the same as that suggested experimentally. The C-13 displacements calculated for these geometries are listed in the middle column of Table II as "the double-layer model". The trends of the characteristic C-13 shifts of the carbons on the two-fold axis(Fig.1A) are satisfactorily reproduced by the calculations, although the agreements of the magnitudes of C-13 displacements are not always good. If we assume that the borderline corresponds to the α -CD's wider rim consisting of secondary hydroxyl groups, the position of the phenyl ring agree well with that found in solution determined by H-1 NMR[5] and that in the solid state by X-ray diffraction[7] for PNP and PHBA,

The theoretical approach which is reported here can not determine from which side of the α -CD cavity the guest molecule is included. The direction of the inclusion, namely, from the wider or narrower side of the α -CD cavity, may be determinable by simple considerations, for example, by building space-filling models, since the major factor determining the inclusion side is considered to be steric acceptability.

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Table II. ^{13}C Chemical Shifts Displacements^a

Compound	Carbon	Calculated		Observed ^d
		Continuum model ^b	Double-layer model ^c	
BA 	C α	-1.00	-1.01	-1.70
	C1	-0.02	-0.14	-1.18
	C2	-0.27	-0.18	1.59
	C3	-0.03	-0.43	-0.76
	C4	-0.24	0.37	0.93
PHBA 	C α	-1.01	-1.02	-1.65
	C1	0.11	-0.07	-0.78
	C2	-0.36	-0.21	1.70
	C3	0.07	-0.57	-0.85
	C4	-0.64	0.45	0.72
PNP 	C4	-0.31	-0.73	-1.21
	C3	-0.54	-0.26	0.87
	C2	-0.07	-1.35	0.23
	C1	-0.85	1.15	1.88

^a Given in ppm. Negative values indicate upfield shifts.

^b Displacements induced by transference of molecule from medium of $\epsilon=80$ to that of $\epsilon=2$.

^c Displacements induced by transference of molecule from medium of $\epsilon=80$ to double-layer of $\epsilon=(80,2)$.

^d α -CD complexation induced shifts cited from Ref. 4.

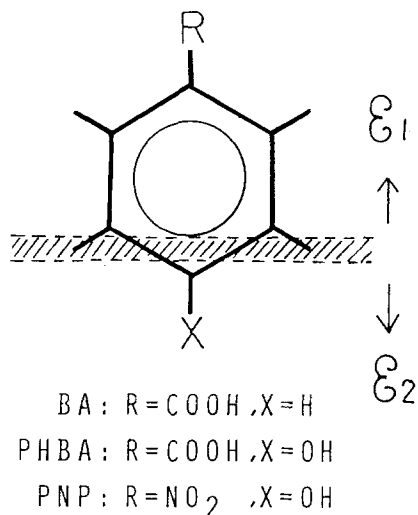


Figure 4. The position of the borderline (shaded region) dividing the surroundings into two layers, ϵ_1 and ϵ_2 , where the characteristic C-13 shift displacements are reproduced by calculations.

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