GEOMETRY OF α-CYCLODEXTRIN INCLUSION COMPLEX WITH m-NITROPHENOL DEDUCED FROM QUANTUM CHEMICAL ANALYSIS OF CARBON-13 CHEMICAL SHIFTS

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ABSTRACT. The host-guest orientation and the position of the guest m-nitrophenol(MNP) in the α-cyclodextrin(α-CD)-MNP inclusion-complex in aqueous solution has been determined by comparing the complexation induced carbon-13 NMR chemical shifts of MNP with those predicted by quantum chemical calculation. In the calculation, the non-polar environmental effect produced by the α-CD cavity on the carbon-13 shifts of included guest molecule has been formulated by the so-called NMR solvent effect theory. Here, carbon-13 shift displacements are assumed to be induced by transference of the guest from polar aqueous phase with higher dielectric constant to the non-polar α-CD cavity with lower dielectric constant. Among a variety of host-guest orientation investigated, only the geometry in which the nitrophenyl group is located in the α-CD cavity and the hydroxyl group is exposed to the aqueous phase can reproduce qualitatively the observed carbon-13 shift displacements of MNP. This geometry is consistent with that in the solid state determined by the X-ray method.

1. INTRODUCTION

High resolution carbon-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 carbon-13 NMR studies of α-CD inclusion complexes with benzoic acid, p-nitrophenol, 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]. Similar distinctive patterns of carbon-13 displacements have been also observed for p-hydroxybenzoic acid and it has been concluded that the carboxyl group of p-hydroxybenzoic acid is directed into the α-CD cavity[4]. A variety of substituted benzenes are known to show quite similar carbon-13 high (head) and low(tail) field shifts, irrespective of the kinds of sub-stituents if their size are matched to the α-CD cavity[4,5]. These characteristic carbon-13 displacements induced by complexation with α-CD
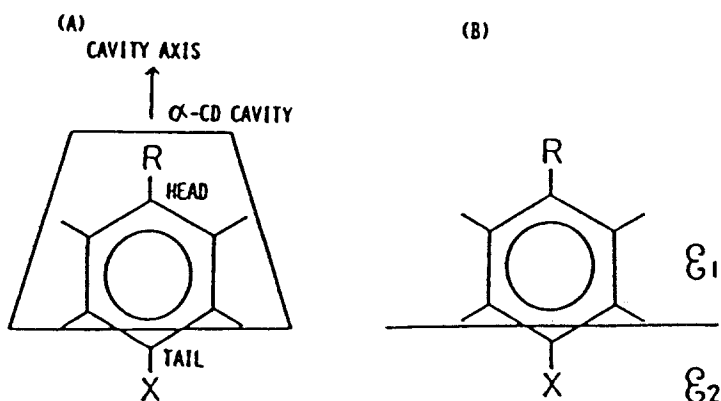
Figure 1. (A) Geometry of α-CD inclusion-complexes with benzene
derivatives. (B) Double-layer model. The benzene derivative is
situated on the borderline dividing the surroundings into two layers of
dielectric constants, ε_1 and ε_2.

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 carbon-13 displacements is accounted for.

In general, there are several kinds of non-bonded interactions,
which may influence the carbon-13 chemical shifts. Among them, the
electrical environmental effects are expected to be the major contri-
bution to the α-CD complexation-induced carbon-13 shifts 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. In the case of
NMR shielding, such environmental effects could be treated as solvent
effects[6].

In a previous report[7], we have successfully applied the quantum
chemical method to the determination of the geometry of α-CD inclusion-
complexes with substituted benzenes such as p-nitrophenol, p-hydroxy-
benzoic acid, and benzoic acid. This method was based on the so-
called solvent-effect theory and it was assumed that the α-CD cavity
has the environmental effect of lower dielectric constant(ε_1) on a
included part of the guest and the other part of guest is exposed to
the aqueous phase of higher dielectric constant(ε_2) as shown in Fig.1B.

In the case of α-CD—m-nitrophenol(MNP) inclusion-complex, there
are two possible geometries as shown in Fig.2. Namely, the first is
that the nitrophenyl group is included and the hydroxyl group is pro-
truded from the α-CD cavity. This structure has been proposed based
on the above-mentioned characteristic carbon-13 shifts of MNP observed
in aqueous solution[4]. X-Ray crystallographic analysis of solid
complex has also support this type of inclusion[8]. The second is the
reverse of the first one, and has been proposed based on also carbon-13
chemical shifts in aqueous solution[9]. Here we tried to determine
the host-guest orientation and position of the guest MNP in the α-CD
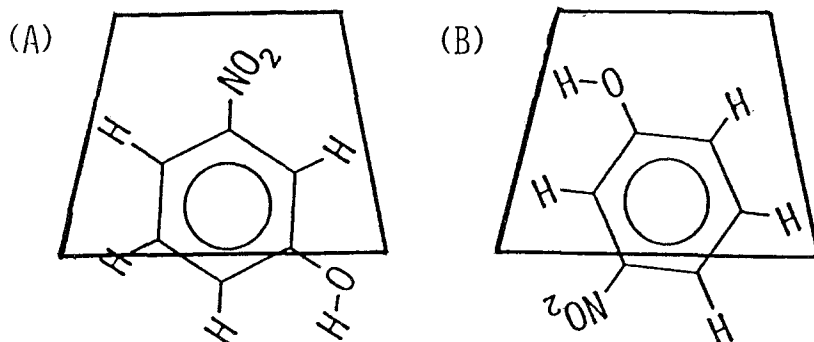inclusion-complex in aqueous solution by the quantum chemical analysis

Figure 2.   Two possible geometries of α-CD—MNP complex.

of carbon-13 chemical shift displacements of
MNP induced by complexation with α-CD.

2.   METHODS
To calculate carbon-13 chemical shifts, we used
the Karplus & Pople's average excitation energy
method using CNDO/2 parameters[10], since this
method was found to give good linearity between
the calculated and observed shifts.   Molecular
orbital calculation were carried out on a HITAC-
M280 computer at the Information Processing
Center of Tokyo Institute of Technology.
As the model of solvent effect on carbon-13
chemical shifts, we used one developed by Ando

M N P

et al.[6] based on a Klopman's "solvaton" theory[11].   This model has
been successfully applied to interpret the dielectric solvent effect on
carbon-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 virtual particle
called a solvaton.   The details of theory and calculation have been
reported[7].   Carbon-13 NMR spectra were recorded at 30 °C on a JEOL
PS-100 spectrometer operated at 25 MHz.
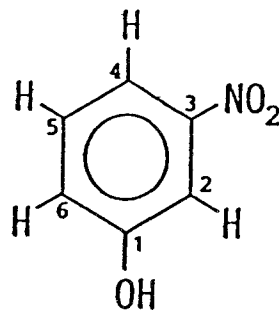
3.   RESULTS and DISCUSSION
In order to take into account the heterogeneous nature of the surround-
ings around the guest molecule in the α-CD inclusion-complex, a realist-
ic solvaton model was constructed.   It was assumed that the α-CD cavity
has the environmental(solvent) effect of dielectric constant 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 assumed
that ε_1 and ε_2 are 2 and 80, respectively.
    The carbon-13 shift displacements were calculated as the function of
the position of the borderline dividing the two layers for a number of
host-guest orientations.   In the calculations, the accurate position

of the border line 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 differ-
ent positions and also by reversing
the orientation of the guest relative
to the α-CD cavity.

By comparing the calculated and
observed carbon-13 displacements, we
tried to determine the geometry of
the inclusion complex. Among a lot
of host-guest geometry investigated,
the observed characteristic carbon-13
shifts, namely, high-field shift of
C-3 resonance and low-field shift of
C-6 resonance, are reproduced at the
same time only when the borderline
is on the shaded region as shown in
Fig.3.   Here, the host-guest
orientation and the position of the
MNP molecule in the α-CD cavity are

Figure 3.   The position of the
borderline(shaded region) di-
viding the surrounding into two
layers, where the characteristic
carbon-13 displacements are re-
produced well by calculations.

the same as that found by X-ray method[8], if we assume that the border
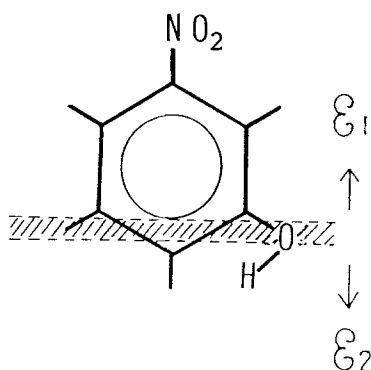line corresponds to the α-CD's wider rim consisting of secondary
hydroxyl groups.

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