Bull. Chem. Soc. Jpn., **62**, 2067—2069 (1989)

A Molecular Orbital Study of Cyclodextrin Inclusion Complexes. II. The Structural Analysis of α-Cyclodextrin Inclusion Complex with *m*-Nitrophenol in Aqueous Solution Based on the Quantum-Chemical Solvation Theory[†,††]

Minoru SAKURAI,* Masaki KITAGAWA, Hajime HOSHI,[†††] Yoshio INOUE, and Richirô CHÛJÔ
Department of Biomolecular Engineering, Tokyo Institute of Technology, O-okayama 2-chome, Meguro-ku, Tokyo 152
(Received December 22, 1988)

Synopsis. The host-guest orientation and the position of the guest *m*-nitrophenol (MNP) in the α-cyclodextrin(α-CD)-MNP complex in aqueous solution have been determined by comparing the complexation-induced ^{13}C NMR chemical shifts of MNP with those predicted by quantum chemical calculation. The results are consistent with the X-ray data of this complex.

α-Cyclodextrins (α-CDs) is a cyclic oligosaccharide composed of six (1—4)-linked α-D-glucosyl residues and admits a variety of guest molecules into its cavity.[1—4)] The inclusion of benzene derivatives has been extensively studied in both solution and solid states.[1—4)] One of the most interesting phenomena observed in such inclusion complexes is the orientational specificity of the guests in the α-CD cavity. For example, in α-CD-*p*-nitrophenol complex, in both solution[5—8)] and solid states[9)] the nitro group is located in the cavity and the phenolic hydroxyl group protrudes from the secondary hydroxyl side of α-CD. The determination of the guest orientation is essential for identifying the main driving force stabilizing the inclusion complexes.[10)]

For α-CD-*m*-nitrophenol complex, two types of guest orientations have been proposed on the basis of the observation of complexation-induced ^{13}C NMR chemical shifts of the guest MNP. Namely, the first (Fig. 2C or D) is that the nitrophenyl group is located in the cavity and the hydroxyl group is exposed to the aqueous medium.[7)] The second (Fig. 2A or B) is the reverse of the first one.[11)] In this report, we show that the first is more reasonable, with the aid of the quantum chemical analysis of ^{13}C chemical shift displacements of MNP.

Methods

In the calculation, the "double layer" model developed in a previous paper[12)] is used in order to approximate the environment surrounding the guest molecule complexed with α-CD. Namely, it is assumed that a part of the guest molecule is embedded in a low dielectric medium (dielectric constant ε_1=2) and its residual part is exposed to the aqueous medium with higher dielectric constant (ε_2=80) as shown in Fig. 1B. Thus the complexation of the guest with α-CD in aqueous solution corresponds to its transfer from the aqueous medium (ε=80) to the double layer one. The interactions of the guest molecule with the dielectrics are formulated on the basis of Klopman's solvation theory.[13)] The molecular wave functions were obtained by means of the CNDO/2 method[14)] and subsequently the ^{13}C shielding constants are evaluated using Karplus and Pople's average excitation method.[15)]

The geometry of MNP was determined using Pople's standard values for bond lengths and bond angles.[14)]

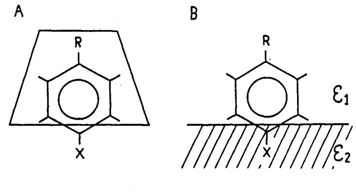

Fig. 1. (A) Schematic representation of α-CD inclusion complexes with benzene derivatives. The CD molecule is represented by bucket-like shape. (B) Double-layer model.

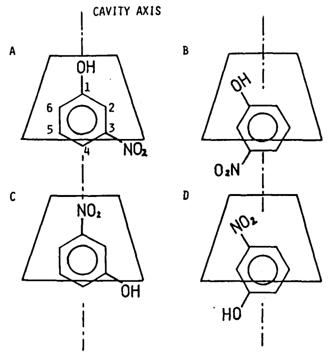

Fig. 2. Possible orientations of the guest MNP relative to the α-CD cavity. Due to the bulkiness of the substituents (NO_2 and OH), only two modes of guest-insertion are possible according to which sustituent is located in the cavity. Furthermore, each of the two is classified into two types of guest-orientations. In the type A and C orientations, the C_3-C_6 axis lies on the cavity one. In type B and D orientations, both the C_4-C_6 and the C_1-C_3 axes are parallel to the cavity axis.

Results and Discussion

According to the preliminary structural analysis using the CPK molecular model, four types of guest

---

[†] Previous paper in series is Ref. 10.

[††] A part of this paper was presented at the 3rd International Symposium on Cyclodextrin, Lancaster, U. K., July, 1986, and the abstract was issued in *J. Inclusion Phenomena*, **5**, 55 (1987).

[†††] Present adress: Institute for Molecular Science, Myodaiji, Okazaki 444.

orientations are possible in the α-CD-MNP complex. They are schematically represented in Fig. 2. For each of these orientations, one can draw the borderline dividing the surrounding of the guest into the two layers and express the depth of guest inclusion as the number of atoms included in the layer of ε_1. A series of calculations of ^{13}C shielding was carried out by shifting the borderline. Then, the complexation-induced ^{13}C shift displacements are expressed as the shift changes when the guest MNP is transferred from the medium of ε=80 to the double-layer environments (ε_1=2, ε_2=80). The calculated results are reproduced in Figs. 3 and 4, where the positive and negative signs for ^{13}C displacements indicate low-field and up-field shifts, respectively and the scale in the abscissa indicates the number of the included atoms mentioned above. The observed data (bold lines) were cited from Ref. 7.

In the case of the type A and C orientations, our attention is particularly given to the carbons lying on the cavity axis: namely the C_1 and the C_4 carbons for the type A orientation and the C_3 and the C_6 carbons for the type C one. In the type B and D orientations, the data for only the C_1, C_3, C_4, and C_6 carbons are examined. These carbons are located far from the cavity interior and thus their ^{13}C shieldings are insusceptible to the so-called steric shielding effects,[12] which are not taken into account in the present theoretical model.

As can be seen from Fig. 3 a (for type A), the calculated values for the C_1 carbon deviate from the corresponding observed ones (bold lines) irrespective of the position of the borderline. Therefore it is impossible to reproduce the observed data for both C_1 and C_4 carbons simultaneously by the calculation. Similarly, in the case of the type B orientation (Fig. 3 b), the calculated values for the C_1 and the C_6 carbons always deviate from the corresponding observed data.

On the other hand, in the cases of the reversed-guest insertions with the type C orientation, the calculated values for both C_4 and C_6 carbons are in excellently good agreement with the corresponding observed ones at the position of 10—12 included-atoms (Fig. 4 a). Similarly, on the assumption of the type D orientation, the calculations simultaneously reproduce the observed trends for the C_1, C_3, C_4, and C_6 carbons at the position of 10 included-atoms, although the agreements of the magnitudes of ^{13}C displacements are not always good.

Therefore, for the α-CD-MNP inclusion complex, the observed characteristic ^{13}C displacements are reproduced only when the guest molecule is inserted into the cavity from the nitro group side (Fig. 2C and D). This orientation of the guest molecule is the same as that found in the solid state by X-ray diffraction for the α-CD-MNP complex.[16] Furthermore, it should be noted that the observed trends are reproduced only at the position of the borderline as shown in Fig. 5. If it is assumed that the borderline corresponds to the α-CD wider rim consisting of secondary hydroxyl groups, one or two carbons in the phenyl ring must protrude from the CD cavity. This finding again agrees with that in the solid state.

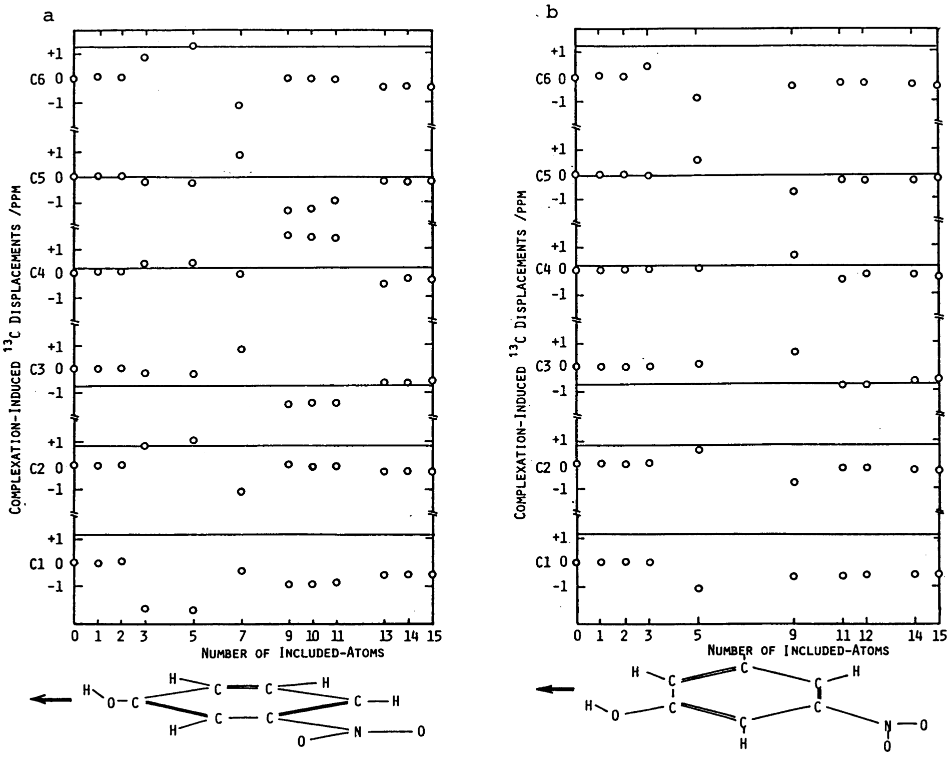

Fig. 3. Dependence of ^{13}C shift displacements of MNP on the position of the borderline. (a) and (b) show the data for the type A and B orientations shown in Fig. 2, respectively. The arrows indicate the direction of guest-insertion.

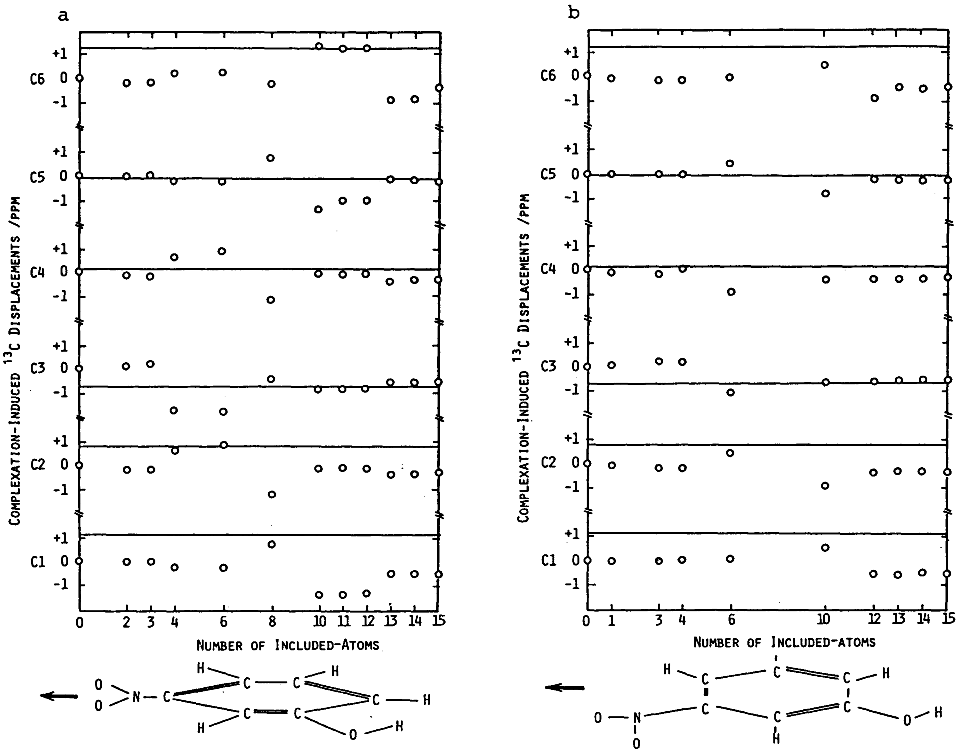

Fig. 4. Dependence of ^{13}C shift displacements of MNP on the position of the borderline. (a) and (b) show the data for the type C and D orientations, respectively.

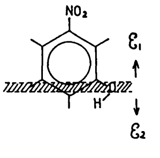

Fig. 5. The position of the borderline (shaded region) where the characteristic ^{13}C displacements are reproduced well by the calculations.

These results are inconsistent with those of Komiyama and Hirai's report.[11] They did not observe the ^{13}C displacements of the tertiary carbons, C_1 and C_3. As described above, these carbons provide decisive information about the orientation of the guest molecule, and thus the lack of these data may be responsible for the discrepancy.

In conclusion, the structure of α-CD-MNP complex in aqueous solution is consistent with that in the solid state.

One (Y. I.) of the authors wishes to thank for the partial support by a Grant-in-Aid for Scientific Research on Priority Area of "Dynamic Interactions and Electronic Processes of Macromolecular Complexes" from the Ministry of Education, Science and Culturee. The authors thank the Computer Center, Institute for Molecular Science, Okazaki National Research Institute, Japan, for the use of the HITAC M-680H and S-810/10 computer system.

References

1) M. I. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag, New York (1978).

2) W. Saenger, *Angew. Chem., Int. Ed. Engl.,* **19**, 344 (1980).

3) I. Tabushi and Y. Kuroda, *Adv. Catal.,* **32**, 417 (1983).

4) Y. Matsui, T. Nishioka, and T. Fujita, *Top. Curr. Chem.,* **128**, 61 (1985).

5) R. J. Bergeron, M. A. Channing, B. Gibeily, and D. M. Pillor, *J. Am. Chem. Soc.,* **99**, 5146 (1977).

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

7) R. I. Gelb, L. M. Schwartz, B. Cardelino, H. S. Fuhrman, R. F. Johnson, and D. A. Laufer, *J. Am. Chem. Soc.,* **103**, 1750 (1981).

8) Y. Yamamoto, M. Onda, M. Kitagawa, Y. Inoue, and R. Chûjô, *Carbohydr. Res.,* **167**, c11 (1987).

9) K. Harata, *Bull. Chem. Soc. Jpn.,* **50**, 1416 (1977).

10) M. Kitagawa, H. Hoshi, M. Sakurai, Y. Inoue, and R. Chûjô, *Bull. Chem. Soc. Jpn.,* **61**, 4225 (1988).

11) M. Komiyama and H. Hirai, *Bull. Chem. Soc. Jpn.,* **54**, 828(1981).

12) Y. Inoue, H. Hoshi, M. Sakurai, and R. Chûjô, *J. Am. Chem. Soc.,* **107**, 2319 (1985).

13) G. Klopman, *Chem. Phys. Lett.,* **1**, 200 (1967).

14) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York (1970).

15) M. Karplus and J. A. Pople, *J. Chem. Phys.,* **38**, 2803 (1963).

16) K. Harata, H. Uedaira, and J. Tanaka, *Bull. Chem. Soc. Jpn.,* **51**, 1627 (1978).