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# RELATIONSHIP BETWEEN THE CYCLODEXTRIN CATALYSES IN THE CLEAVAGES OF PHENYL ACETATES AND THE TIME-AVERAGED CONFORMATIONS OF THE INCLUSION COMPLEXES

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The time-averaged position of p-nitrophenyl acetate, phenyl acetate, or m-nitrophenyl acetate in the cavity of α-cyclodextrin is determined in the 1:1 mixture of dimethyl sulfoxide and water by $^{1}$H-NMR spectroscopy. The magnitude of the acceleration of the cleavage of these substrates by α-cyclodextrin increases with the decrease of the distance between the carbonyl carbon atom of the substrate and the O-2 atom of α-cyclodextrin.

Specificity is one of the characteristics of the cyclodextrin-catalyzed reactions. Although it has been widely accepted that the specificity derives from the difference of the structure of the inclusion complex between cyclodextrin and the substrate,[1] detailed analyses on the origin of the specificity have not been made, probably because of the scant information on the structures of the inclusion complexes in solution.

In the previous papers,[2,3] the time-averaged positions of aromatic guest compounds in the cavity of cyclodextrin in aqueous solutions were determined by fitting the changes of the $^{1}$H-NMR chemical shifts of the H-3 and H-5 atoms of cyclodextrin to the calculated values of the anisotropic shielding effects of the aromatic rings of the guest compounds. Furthermore, the much larger magnitude of the acceleration of the cleavage of m-t-butylphenyl acetate by β-cyclodextrin than that of p-t-butylphenyl acetate was satisfactorily interpreted in terms of the time-averaged conformations of the inclusion complexes estimated under the assumption that the time-averaged positions of the aromatic rings of the acetyl esters in the cavity of β-cyclodextrin were identical with those of the corresponding phenols.[3]

In this paper, the time-averaged positions of the aromatic substrates, p-nitrophenyl acetate, phenyl acetate, and m-nitrophenyl acetate in the cavity of α-cyclodextrin are directly determined in the 1:1 (v/v) water-dimethyl sulfoxide solution in a similar way. The use of this solvent system instead of water is necessary because of the poor solubilities of these substrates in water. The relationship between the time-averaged positions of the substrates and the magnitudes of the acceleration of their cleavages by α-cyclodextrin, determined in the water-dimethyl sulfoxide mixture of the same composition, is described.

The time-averaged positions of the phenyl acetates were determined according to the previous method [2] briefly described as follows.

1) The changes of the chemical shifts of the H-3 and H-5 atoms of α-cyclodextrin on its complex formation with the phenyl acetates were experimentally determined.
2) The magnitudes of the anisotropic shielding effects by the aromatic rings of the guest compounds on the H-3 and H-5 atoms were evaluated by use of the table by Johnson and Bovey.[4]
3) The optimal position of the aromatic ring was determined by shifting the center of the aromatic ring along the longitudinal axis of the cavity of α-cyclodextrin. At the optimal position, the agreements between the observed values of the chemical shift

changes and the calculated values of the anisotropic shielding effects for both the H-3 and H-5 atoms were maximal. The optimal position was taken as the time-averaged position of the aromatic ring of the phenyl acetate.

The $^1$H-NMR spectra were measured in the 1:1 (v/v) mixture of 1 N deuterium chloride and dimethyl sulfoxide-$d_6$ on the JEOL PS-100 spectrometer at ambient temperature (around 25°C). The chemical shifts were determined by using dimethyl sulfoxide as the internal reference. Kinetic studies were made at 25°C in the 1:1 (v/v) mixture of pH 8.5 aqueous buffer and dimethyl sulfoxide by using the absorption spectroscopy.

The chemical shifts of the protons of α-cyclodextrin in the 1:1 water-dimethyl sulfoxide solution were identical with those in the aqueous solution within experimental error. This result indicates the absence of significant changes of the chemical shifts due to the specific interactions between α-cyclodextrin and dimethyl sulfoxide, and thus shows the applicability of the present method, devised for the study of the inclusion complexes in aqueous solutions, to the study of the inclusion complexes in the water-dimethyl sulfoxide solution.

Figure 1 depicts the time-averaged positions of the phenyl acetates in the cavity of α-cyclodextrin, determined by the $^1$H-NMR spectroscopy. In these time-averaged conformations, the centers of the aromatic rings of p-nitrophenyl acetate, phenyl acetate, and m-nitrophenyl acetate, respectively, are at the heights of 2.2, 1.9 and 1.7 A with respect to the plane comprised of the six H-3 atoms of α-cyclodextrin. As shown in Table 1, the calculated values of the anisotropic shielding effects of the aromatic rings of the phenyl acetates on both the H-3 and H-5 atoms fairly agree with the observed values.

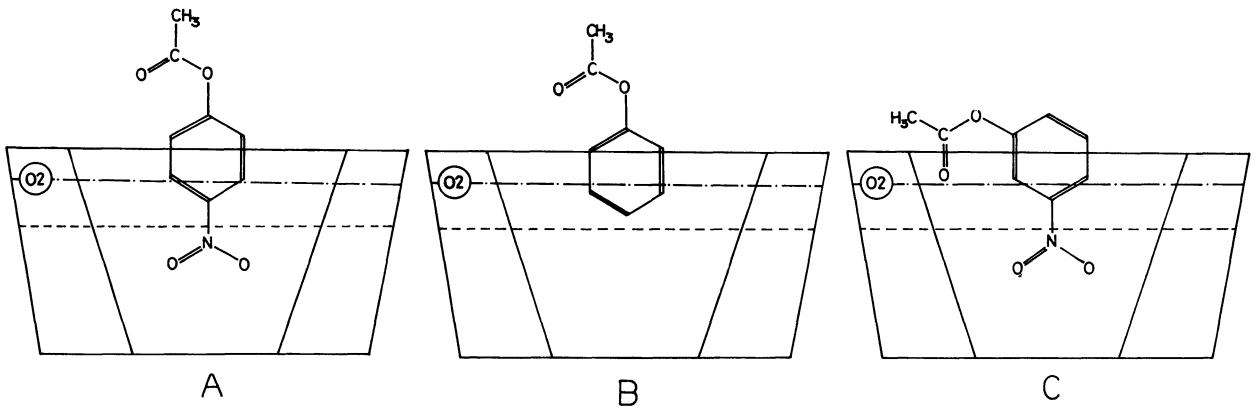


Figure 1 Time-averaged conformations of the inclusion complexes of α-cyclodextrin with p-nitrophenyl acetate (A), phenyl acetate (B), and m-nitrophenyl acetate (C) in the 1:1 (v/v) mixture of 1 N deuterium chloride and dimethyl sulfoxide; ----- and —•—, respectively, refer to the planes comprised of the six H-3 and O-2 atoms of α-cyclodextrin; (O2) shows the position of one of the six O-2 atoms.

Table 1 Observed and calculated values of the $^1$H-NMR chemical shift changes on the complex formation of α-cyclodextrin with phenyl acetates [a]

| Substrate | Change of the $^1$H-NMR chemical shift (ppm) [b] | | | |
|---|---|---|---|---|
| | H-3 | | H-5 | |
| | obsd | calc | obsd | calc |
| p-Nitrophenyl acetate | 0.00 | 0.00 | -0.06 | -0.07 |
| Phenyl acetate | +0.04 | +0.04 | -0.04 | -0.07 |
| m-Nitrophenyl acetate | +0.06 | +0.06 | -0.06 | -0.08 |

a. In the 1:1 (v/v) mixture of 1 N deuterium chloride and dimethyl sulfoxide-$d_6$.
b. The positive sign refers to the increase in the shielding.

In these conformations, the acetyl groups protrude from the secondary hydroxyl side of the cavity, since the α-cyclodextrin-accelerated cleavages proceed via the nucleophilic attack of the O-2 atoms in the secondary alkoxide ion of α-cyclodextrin at the carbonyl carbon atoms of the substrates.[1] The complex in which the acetyl group penetrates in the cavity as a head is non-productive because of the drastic strains in chemical bonds induced on the nucleophilic reactions.[5] The nitro group is located so that its symmetry axis coincides with the longitudinal axis of the cavity of α-cyclodextrin. The movement of the nitro group inside the cavity is rather restricted, since the size of the nitro group fits considerablly well to the size of the cavity of α-cyclodextrin.

Table 2 shows the distances between the carbonyl carbon atoms, the electrophilic centers, and the ring comprised of the six O-2 atoms of α-cyclodextrin, the nucleophilic centers, estimated from the time-averaged conformations in Figure 1. The distance for the α-cyclodextrin-m-nitrophenyl acetate complex was determined by assuming that the bond between the ethereal oxygen atom and the aromatic ring in the substrate rotates rather freely. In the complexes of α-cyclodextrin with p-nitrophenyl acetate and phenyl acetate, the rotations around the corresponding bonds have no effects on the distances between the carbonyl carbon atoms and the ring comprised of the six O-2 atoms.

Table 2 Distances between the carbonyl carbon atoms of the phenyl acetates and the O-2 atoms of α-cyclodextrin and the magnitudes of the acceleration of the cleavages of the phenyl acetates by α-cyclodextrin

| Substrate | Distance (A) [a] | Magnitude of acceleration [b] |
|---|---|---|
| p-Nitrophenyl acetate | 6.0 | 4.4 |
| Phenyl acetate | 5.8 | 14 |
| m-Nitrophenyl acetate | 3.4 | 220 |

a. The distances between the carbonyl carbon atoms of the substrates and the ring comprised of the six O-2 atoms of α-cyclodextrin are determined from the time-averaged conformations (Figure 1) in the 1:1 (v/v) mixture of 1 N deuterium chloride and dimethyl sulfoxide-$d_6$.
b. The ratios of the rate constants of the cleavages of the substrates incorporated in the α-cyclodextrin inclusion complexes to those in the absence of α-cyclodextrin are determined kinetically in the 1:1 (v/v) mixture of pH 8.5 buffer and dimethyl sulfoxide.

In Table 2, the magnitudes of the acceleration of the cleavages of the phenyl acetates (the ratios of the rate constants for the substrates incorporated in the α-cyclodextrin complexes to those in the absence of α-cyclodextrin), kinetically determined in the 1:1 mixture of pH 8.5 buffer and dimethyl sulfoxide by the usual method,[1] are also shown.

The magnitude of the acceleration by α-cyclodextrin was definitely governed by the distance between the nucleophile and the electrophile. The order in the increase of the magnitude of the acceleration (m-nitrophenyl acetate≫phenyl acetate>p-nitrophenyl acetate) is identical with that in the decrease of the distance between the carbonyl carbon atom and the O-2 atom.

The strong dependence of the acceleration on the distance is associated with the change of the conformation of the inclusion complex in the course from the initial state to the transition state. The conformational change makes the access of the carbonyl carbon atom to the O-2 atom possible so that the nucleophilic reaction can result in the formation of the tetrahedral intermediate.[6] The conformational change should accompany an increase in the enthalpy, since the driving force of the formation of the inclusion complex is the decrease of the enthalpy.[1] Thus, the conformational change partially compensates the decrease of the activation enthalpy coming from the loss of the translational and rotational entropy due to the complex formation between α-cyclodextrin and the substrate prior to the chemical transformation. When no conformational change takes place during the reaction, the loss of the entropy by the complex formation of the substrate and the catalyst shows up as the decrease of the activation enthalpy, because of the structural changes of the water molecules around the substrate and the catalyst.[7] An inclusion complex with a smaller distance, which requires a smaller conformational change, shows larger acceleration because of the large magnitude of the decrease of the activation enthalpy. This argument is supported by the thermodynamic study [8] showing that the magnitude of the acceleration by α-cyclodextrin increased with the decrease of the activation enthalpy rather than with the increase of the activation entropy.

In conclusion, the specificity in the α-cyclodextrin-accelerated cleavage of phenyl acetates comes from the difference in the distance between the nucleophile and the electrophile in the inclusion complex. The difference in the distance shows up as the difference in the activation enthalpy due to the changes of the conformations of the inclusion complexes during the reactions.

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