CHEMISTRY LETTERS, pp. 1467-1470, 1980.

TIME-AVERAGED CONFORMATIONS OF THE INCLUSION COMPLEXES OF β-CYCLODEXTRIN WITH t-BUTYLPHENOLS

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Time-averaged position of phenol, p-t-butylphenol or m-t-butyl phenol in the cavity of β-cyclodextrin in aqueous solution is determined by using the ^{1}H-NMR spectroscopy. The order of the rate constants of the β-cyclodextrin-accelerated cleavages of the corresponding acetyl esters is satisfactorily interpreted in terms of the time-averaged positions of the substrates estimated from those of the phenols.

The catalyses by cyclodextrins show many specificities, since they involve the complex formation of the substrate with the cyclodextrins prior to the chemical transformation.$^{1)}$ Of many specificities exhibited by cyclodextrins, the meta-para specificity in the hydrolyses of phenyl acetates is one of the most striking ones. Here the meta-para specificity means that the cleavage of the meta-substituted phenyl acetate is accelerated by α- and β-cyclodextrins in much a larger extent than that of the corresponding para-compound.$^{2)}$ The magnitude of the acceleration for unsubstituted phenyl acetate is between those of the meta- and the para-compounds.$^{2)}$ The meta-para specificity was attributed to the difference in the distance between the nucleophile, the secondary alkoxide ion of cyclodextrins, and the electrophile, the carbonyl carbon atom of the substrate on the basis of the study using the Corey-Pauling-Koltun molecular model.$^{2)}$ However, the distance estimated in this way is not confirmative, since the positions of the substrates in the cavity, that is, the depths of the penetration of the substrates are arbitrary.

In a previous paper, the time-averaged positions of p-nitrophenol and benzoic acid as well as their anions in the cavity of α-cyclodextrin were determined by using the magnitudes of the anisotropic shielding effects of the aromatic rings of the guest compounds on the protons of α-cyclodextrin.

In the present paper, the time-averaged positions of phenol, p-t-butylphenol, and m-t-butylphenol in the cavity of β-cyclodextrin in aqueous solution are determined in a similar way by the ^{1}H-NMR spectroscopy. Furthermore, the time-averaged positions of the corresponding acetyl esters, phenyl acetate, p-t-butylphenyl acetate, and m-t-butylphenyl acetate, are estimated from those of the phenols. The relationship between the time-averaged positions of the acetyl esters in the cavity and the rate constants of the β-cyclodextrin-accelerated cleavages of them will shed light on the origin of the meta-para specificity.

The calculation of the magnitudes of the shielding effects (Δ_{calc}'s) of the aromatic ring on the H-3 and H-5 protons of β-cyclodextrin (see Fig. 3) was made by use of the table by Johnson and Bovey $^{4)}$ under the following assumptions:

1) The distances of the H-3 and H-5 atoms from the longitudinal axis (z-axis as shown in Fig. 3) of the cavity of β-cyclodextrin are 4.1 and 3.4 A, respectively, as shown by the study using a Corey-Pauling-Koltun molecular model,

2) The center of the aromatic ring of the guest compound is on the z-axis, and

3) The aromatic ring takes the conformation shown in Fig. 1.

The third assumption is reasonable, since the rotation of the aromatic ring around the z-axis by 25.7° results in the identical conformation, and the change of Δ_{calc} during the rotation by this magnitude of degree is at most 0.03 ppm. The Δ_{calc} of the H-3 or H-5 atoms was obtained by averaging the seven values of the shielding effects, each of which corresponds to one of the seven glucose units of β-cyclodextrin. The optimal position of the guest compound was determined by shifting the aromatic ring along the z-axis. At the optimal position, Δ_{calc}'s show the maximal agreements with corresponding observed values (Δ_{obs}'s) for both the H-3 and H-5 atoms. The position was taken as the time-averaged position. Analyses on the protons of β-cyclodextrin other than the H-3 and H-5 ones were not attempted, since they were so far away from the guest compounds that the table in ref. 4 was not applicable.

Figure 2 shows the dependence of Δ_{calc} on the distance between the center of the aromatic ring and the plane comprised of the corresponding seven protons of β-cyclodextrin.

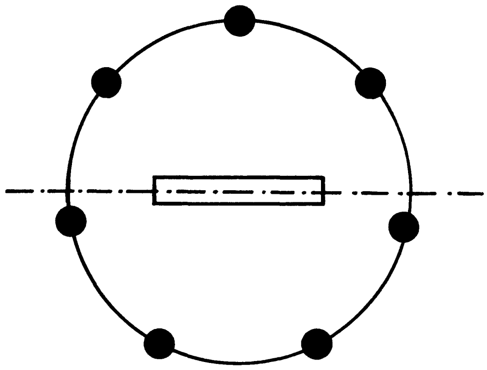

Fig. 1 Conformation of the inclusion complexes used for the calculation of Δ_{calc}; the black circles and the rectangle, respectively, refer to the positions of the H-3 or H-5 atoms of β-cyclodextrin and the orientation of the aromatic rings of phenols.

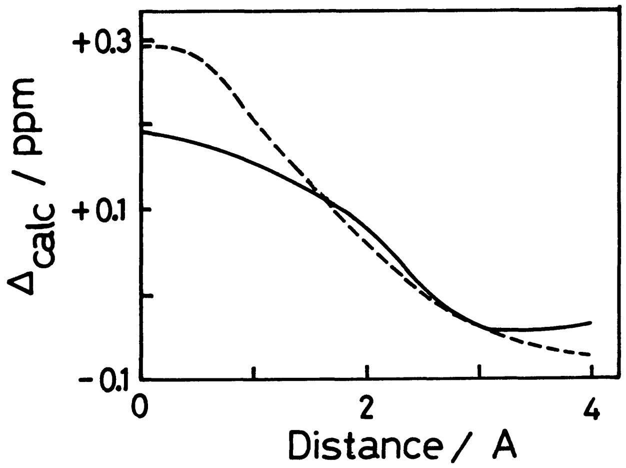

Fig. 2 Plots of the magnitudes of the shielding effects of an aromatic ring (Δ_{calc}) on the H-3 atoms (the solid line) and the H-5 atoms (the dotted line) vs the distance between the center of the aromatic ring and the plane comprised of the corresponding seven protons of β-cyclodextrin ; the positive sign shows the increase of the shielding.

In Fig. 3, the time-averaged positions of the aromatic rings of the phenols in the cavity of β-cyclodextrin are depicted. With respect to the plane comprised of the seven H-3 atoms of β-cyclodextrin, the centers of the aromatic rings of phenol, p-t-butylphenol , and m-t-butylphenol are located at the depths of +1.7, +0.2, and +1.1 A, respectively. Here, the positive sign refers to the region in the side of the primary hydroxyl groups of β-cyclodextrin. In these time-averaged conformations, the agreements between the Δ_{calc}'s and Δ_{obs}'s for both the H-3 and H-5 atoms are satisfactorily fair as shown in Table 1.

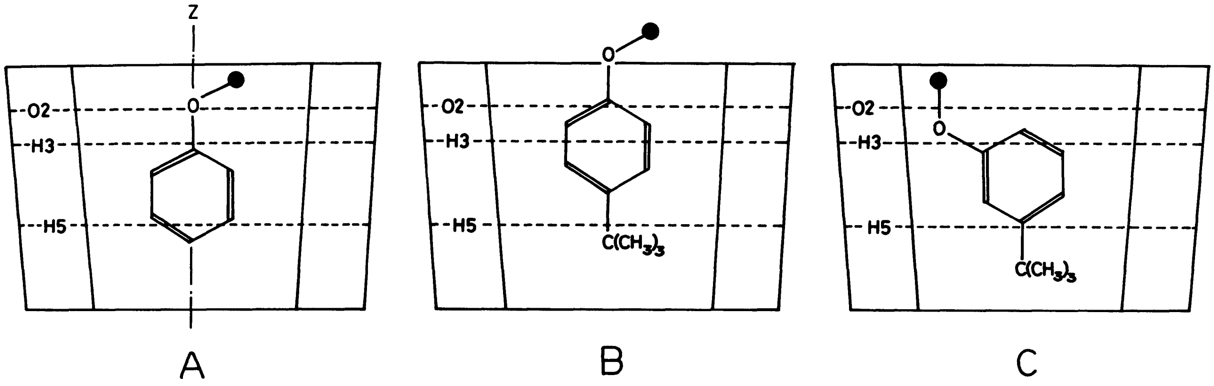

Fig. 3 Time-averaged conformations of the inclusion complexes of β-cyclodextrin with phenol (A), p-t-butylphenol (B) and m-t-butylphenol (C); the black circles show the positions of the carbonyl carbon atoms of the phenyl acetate, p-t-butylphenyl acetate, and m-t-butylphenyl acetate, determined by assuming that the positions of the aromatic rings are identical with those of the corresponding phenols; ---H3--- , ---H5---, and ---O2--- represent the planes comprised of the corresponding seven atoms of β-cyclodextrin.

Table 1 Values of Δ_{calc} and Δ_{obs} for the inclusion complexes of β-cyclodextrin with phenol, p-t-butylphenol, and m-t-butylphenol

Guest Compound	Protons of β-Cyclodextrin	Δ_{calc} (ppm)	Δ_{obs} (ppm)[a]
Phenol	H-3	+0.10	+0.09
	H-5	+0.26	+0.26
p-t-Butylphenol	H-3	+0.19	+0.21
	H-5	+0.02	+0.03
m-t-Butylphenol	H-3	+0.16	+0.20
	H-5	+0.16	+0.20

a. From P. V. Demarco and A. L. Thakkar, Chem. Commun., 1970, 2.

The black circles in Fig. 3 refer to the positions of the carbonyl carbon atoms of phenyl acetate, p-t-butylphenyl acetate, and m-t-butylphenyl acetate, determined under the assumption that the positions of the aromatic rings of these acetyl esters are identical with those of the corresponding phenols. The aromatic rings of the acetyl esters (as well as those of the phenols) have considerably poor freedom with respect to the movements in their molecular planes because of the fitness of the molecular sizes of them with the size of the cavity of β-cyclodextrin, although they are rather free in the rotation around the z-axis.

Table 2 shows the distances between the carbonyl carbon atoms of the acetyl esters and the ring comprised of the seven O-2 atoms of β-cyclodextrin as well as the magnitudes of the accelerations of the cleavages of them by β-cyclodextrin. The O-2 atoms (in the secondary alkoxide ions of β-cyclodextrin) are the nucleophiles in the β-cyclodextrin-accelerated cleavages. Obviously, the order of the magnitude of the acceleration is identical with the order in the decrease of the distance between the nucleophilic center (the O-2 atom) and the electrophilic center (the carbonyl carbon atom). Thus, the larger acceleration for the meta-compound than the para-compound is attributable to the orientation of the nucleophilic and electrophilic centers appropriate for the reaction.

Table 2 Distance between the carbonyl carbon atom of phenyl acetate, p-t-butylphenyl acetate or m-t-butylphenyl acetate and the O-2 atom of β-cyclodextrin as well as the magnitudes of the accelerations of the cleavages of them by β-cyclodextrin

Substrate	Distance between the nucleophilic and electrophilic centers (A) [a]	Magnitude of the acceleration by β-cyclodextrin [b]
Phenyl Acetate	5.1	9.5
p-t-Butylphenyl Acetate	5.6	2.5
m-t-Butylphenyl Acetate	4.0	270

a. Distances between the carbonyl carbon atom and the ring comprised of the seven O-2 atoms of β-cyclodextrin.

b. The ratio of the rate constant of the cleavage of the substrate incorporated in the inclusion complex to that in the absence of cyclodextrin, determined at pH 10.6, 25°C.

The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

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(Received August 1, 1980)