CHEMISTRY LETTERS, pp. 2227-2230, 1990.

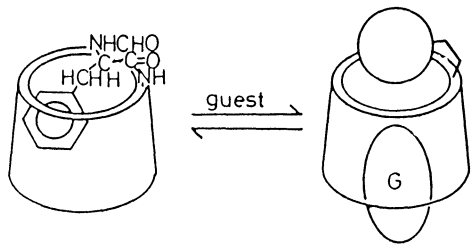
Enantioselective Inclusion Behavior of Monosubstituted Cyclodextrins with Guest-Induced Substituent Movement

Keiko TAKAHASHI,* Yutaka OHTSUKA, and Kenjiro HATTORI
Department of Industrial Chemistry, Faculty of Engineering,
Tokyo Institute of Polytechnics, Atsugi, Kanagawa 243-02

6N(N'-formyl-D- and L-phenylalanyl)-deoxyamino-β-cyclodextrins(I and II) indicate reversed enantiomeric selectivity when they include D- and L-dansylphenylalanine.

Efforts have recently been made to modify cyclodextrins(CD) so as to enhance their catalytic powers or molar recognition ability.[1] There are a growing number of reports of the successful use of CDs to achieve kinetic resolutions of racemic substrates[2] or optical induction in reactions involving prochiral centers.[3] Tabushi and his coworkers introduced two cooperating functional groups to the C6 position of CD in an appropriate spatial arrangement and have estimated the association constants for the D- or L-tryptophan.[4] The ratio of the association constant for the D- and L-form was about 1.3. Ueno and his coworkers have described that azobenzene capped cyclodextrin, which forms 1:2 host-guest complexes, exhibits chiral recognition in including second guest molecules.[5] They also have prepared some modified CDs, which have a naphthalene,[6] anthracene,[7] pyrene,[8] or dansyl unit.[9] These new hosts show remarkable molecular recognition in guest binding. In the latter modified CDs, the substituent was included in its own cavity, and actually observed guest-induced variations in circular dichroism or fluorescence spectra. Recently, we have prepared the new host compounds, 6N(N'-formyl-D- and L-phenylalanyl)deoxyamino-β-CD(I and II)[10] and 6N(N'-formyl-D- and L-phenylglycyl)deoxyamino-β-CD(III and IV). NMR measurements suggested that I and II include the covalently bound phenyl moiety in their own cavity(Fig.1a,4b) to form an intramolecular host-guest complex. Moreover, the association constants of I and II for the same guest are very different. We have examined the new hosts' inclusion abilities, they exhibit enantioselectivity in the inclusion of optical isomers of dansyl amino acids(Fig. 2) with guest-induced substituent movement.

I, II, III,and IV were prepared from 6-monodeoxyamino-β-CD and N-formyl-D or L-amino acids in the presence of DCC according to our previous



1a 1b

Fig. 1. The shape of new host in the presence(b) and absence(a) of guest molecule.

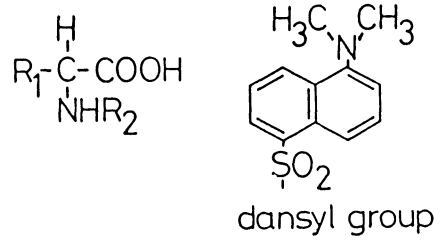


Fig. 2. Various guest molecules;dansyl-Phe:R_1= $C_6H_5CH_2$,R_2=dansyl,dansyl-Ala: R_1=CH_3, R_2=dansyl.

letter.[10] The D- and L-dansyl amino acids were prepared from each amino acid and dansyl chloride and purified by column chromatography. The chemical and enantio purity of these guests were checked by HPLC attached with an Enantio L1 column(TOSO). The association constants K for the molecules with a dansyl moiety were obtained from fluorescence spectra originating from their dansyl moieties. The K values for other nonfluorescent guest were obtained by a previously reported method,[11] using ANS as a fluorescence probe.

The fluorescence intensities of I, II and formyl-L-phenylalanine(f-L-Phe) in aqueous solution are different though the solution contained the same concentration of chromophore. The quantum yields of I, II,and f-L-Phe are 0.45, 0.30,and 0.08, respectively(referred to as quinine sulfate). This resultindicates that the fluorescence of f-Phe moiety staying in the hydrophobic environment is stronger than that in aqueous solution. Fig.3 shows the fluorescence spectra of II in the presence and absence of cyclohexanol. This guest-induced variation in fluorescence intensitysuggests that the f-Phe moiety moves from the interior of the hydrophobic cavity toward the bulk water environment outside the cavity. NMR measurement with 500 MHz also indicates the guest-induced movement of f-Phe moiety(Fig.4). In the presence of guest molecules, the characteristic phenyl proton signals caused by intramolecular complex formation could not observed. The phenyl proton signals of III and IV were found in three groups, almost the same as the signals of formylphenylglycyne both in the absense and presence of guest molecules. The phenyl moiety of III and IV should not be included in their own cavity and stay outside

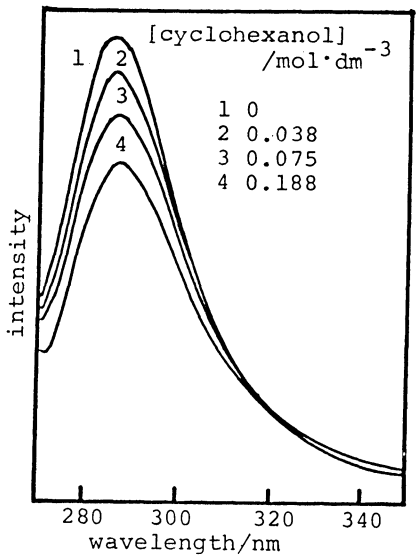


Fig. 3. Fluorescence spectra of II(3.0×10^{-4}M) in pH7.0 aqueous solution. Excitation wavelength was 260 nm.

the cavity.

The above structural characteristics caused the remarkable enantioselective recognition. The results are summarized in Table 1. The data indicate that; (A) I and II exhibit enantiomeric recognition when including dansylphenylalanine,(B)the enantioselectivity of I is reversed compared with that of II, (C)the dansylated guest is included more strongly than the formylated guest, but enantioselectivity is not observed when only the dan-

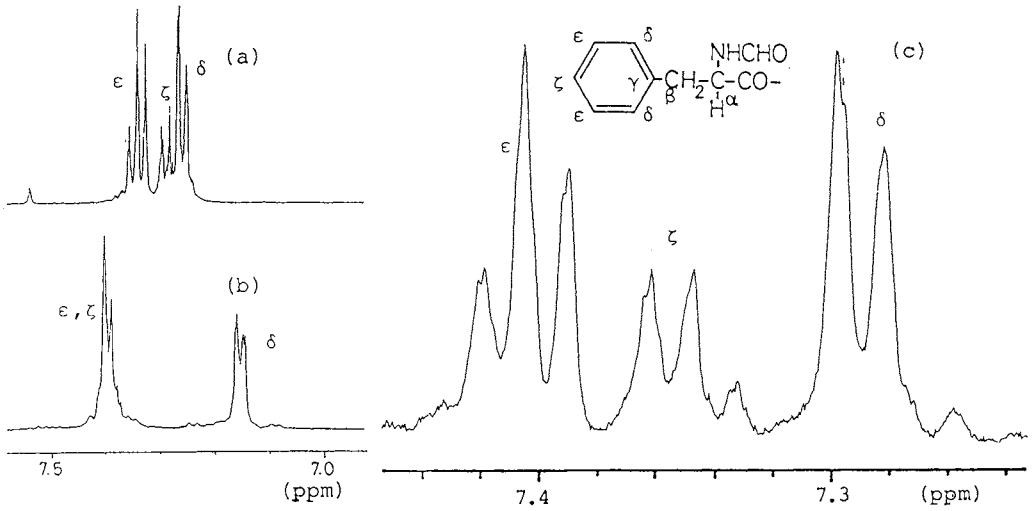


Fig. 4. 500 MHz NMR Spectra of f-L-Phe(a) and II in the absence(b) and presence(c) of cyclohexanol in D_2O.

Table 1. Association constants [a)]

Host	Guest($K/M^{-1}=mol^{-1}\cdot dm^3$)					
	dansyl-phenylalanine[b)]		formyl-phenylalanine[c)]		dansylalanine[c)]	
	D	L	D	L	D	L
I	160±36	83±28	-[d)]	-[d)]	42±13	54±10
(K_D/K_L)[e)]	(2.0)		(-)		(0.9)	
II	139±24	231±45	-[d)]	-[d)]	113±18	95±17
K_D/K_L)[e)]	(0.6)		(-)		(1.2)	
β-CD	197±20	153±14	41±1	35±0	179±13	144±13
(K_D/K_L)[e)]	(1.2)		(1.2)		(1.2)	

a) Determined at 520 nm fluorescence intensity excited at 335 nm in pH 7.0 phosphate buffer 2t 25 °C except for f-Phe. b) This work. c) Ref. 10. d) The value was too small to be determined. e) The ratio of association constants between the D form and L form of the guest molecule.

syl moiety is present. The data suggest that the dansyl moiety is bound in the CD's cavity, and the differences in relative positions of the phenyl and dansyl rings within the chiral guest molecules are recognized by I or II. We had indicated previously[10] that both I and II hardly include the guest molecules of a common size. The cavity of I or II is too narrow to include guest molecules because they include their f-Phe moiety. As is shown in Figs. 3 and 4, when the intermolecular guest molecules is included, intramolecular f-Phe moves from the interior toward outside of the hydrophobic cavity. This movement was occurred basis on the balance between binding ability of the guest molecules and f-Phe moiety covalently bound to I or II. As the guest molecules of a common size have almost the same binding ability to β-CD as intramolecular f-Phe, the f-Phe did not move. The dansyl moiety, with a high binding ability to β-CD can be included in the cavity of I or II. These inclusions in competition with intramolecular complex formation cause high molecular recognition. III and IV without formation of intramolecular complex and guest-induced movement indicate lower molecular recognition than I and II and did not reversed enantiomeric selectivity (III;K_D:505±70, K_L:368±53, IV;K_D:381±52, K_L:262±56 M^{-1}). The enantioselectivity observed here may arise from the interactions of guest molecules with the host molecule rim or its wall consisting of CD and phenylalanine(Fig.1b);the CD wall and rims of I and II exert opposing effects with each other in recognition of the guest chirality.

References

1)A.Croft and R.A.Bartsch, Tetrahedron, 39, 1417(1983);R.Breslow, Science, (Washington,DC)1982,218,532.
2)G.L.Trainor and R.Breslow, J.Am.Chem.Soc., 103, 154 (1981).
3)Fornasier, F.Reniero, P.Scrimin, and U.Tonellato, J.Org.Chem.,50,3209 (1985).
4)I.Tabushi, Y.Kuroda, and T.Mizutani, J.Am.Chem.Soc., 108,4514(1989).
5)A.Ueno, K.Takahashi, R.Saka, and T.Osa, Heterocycles,15,671(1981).
6)A.Ueno, F.Moriwaki, T.Osa, F.Hamada, and K.Murai, Tetrahedron, 43,1571 (1987).
7)A.Ueno, F.Moriwaki, A.Azuma, and T.Osa, J.Org.Chem., 54, 295 (1989).
8)A.Ueno, I.Suzuki, and T.Osa, Chem.Lett., 1989, 1059.
9)A.Ueno, S.Minato, I.Suzuki, M.Fukushima, M.Ohkubo, T.Osa, F.Hamada, and K.Murai, Chem.Lett., 1990, 605.
10)K.Takahashi, Y.Ohtsuka, S.Nakada, and K.Hattori, J.Inclusion Phenomena, in press; W.Saka, Y.Yamamoto, Y.Inoue, R.Chujo, K.Takahashi, and K. Hattori, Bull.Chem.Soc.Jpn., in press.
12)H.Kondo, H.Nakatani, and K.Hiromi, J.Biochem.(Tokyo), 79, 393 (1976).

(Received September 21, 1990)