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COMPLEX FORMATION OF MODIFIED CYCLODEXTRINS WITH ORGANIC SALTS IN ORGANIC SOLVENTS

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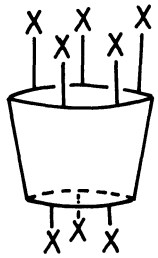
Heptakis(2,3,6-tri-O-acetyl)-β-cyclodextrin and heptakis-(2,3,6-tri-O-phenylcarbamoyl)-β-cyclodextrin form complexes in chloroform and benzene with various ammonium, alkali metal, and alkaline earth metal salts of 2,4,6-trinitrophenol, 4-nitrophenol, methyl orange, and patent blue. The magnitude of complex formation largely depends on the metal cation of the salt.

Cyclodextrins have been widely used as models of enzymes[1,2] and catalysts for organic syntheses.[3-6] The specific catalyses by these cyclic oligomers of glucose, are definitely attributed to complex formation of them with reagents prior to chemical transformation.

Up to date, only three solvents, water, dimethyl sulfoxide,[7] and dimethylformamide,[7] have been successfully used as solvents for the reactions involving cyclodextrins or their derivatives. In other solvents, they show no complex formation with guest compounds. Thus, discovery of new solvents available can extend the spectrum of their application.

In this paper, it will be shown that heptakis(2,3,6-tri-O-acetyl)-β-cyclodextrin (1) and heptakis(2,3,6-tri-O-phenylcarbamoyl)-β-cyclodextrin (2) effectively form complexes with various organic salts in chloroform and benzene.



1 : X = $-O-\overset{O}{\overset{\|}{C}}CH_3$

2 : X = $-O-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-C_6H_5$

1 and 2, respectively, were synthesized by the reactions of β-cyclodextrin with acetic anhydride and phenyl isocyanate, and were repeatedly recrystallized from ethanol-water and from 2-propanol; 1, mp 195-196 °C (lit,[8] 195 °C); 2, mp 215-218 °C (lit,[9] 214-218 °C).

Complex formation of various salts with 1 or 2 in chloroform or benzene was investigated with the use of increase in the solubility of these salts on the

Table 1. Solubility of salts of 2,4,6-trinitrophenol in chloroform with and without 1 or 2 [a]

Cation in the salt	Solubility (10^{-2} mM) [b]			Molar ratio of the complexed salt to the charged 1 or 2 (%) [c]	
	with 1	with 2	without 1 or 2	1	2
NH_4^+	2.1	10.8	0.0	0.8	4.3
	1.6 [d]		0.0 [d]	0.6 [d]	
Ca^{2+}	143	244	0.7	56.9	97.3
	28 [d]		0.0 [d]	11.2 [d]	
Ba^{2+}	15.8	67.6	0.2	6.2	27.0
Li^+	40.6	191	1.7	15.6	75.7
Na^+	1.2	56.8	0.0	0.5	22.7
	0.5 [d]		0.0 [d]	0.2 [d]	
K^+	1.0	10.2	0.0	0.4	4.1
Cs^+	0.3	0.5	0.0	0.1	0.2

a) 30 °C; $[1]_0 = [2]_0 = 2.5$ mM.
b) Average of the values for duplicate or triplicate measurements, which coincide with each other within ±2%.
c) The ratio of the increase in solubility by the addition of 1 or 2 vs. the charged concentration of 1 or 2.
d) Benzene was used as solvent in place of chloroform.

addition of 1 or 2. Chloroform or benzene (10 ml) containing a required amount of 1 or 2 was incubated with excess amount of solid salt at 30 °C for 24 h, during which the specimen was vigorously shaken. The concentration of the salt dissolved in the organic solvent was determined by absorption spectroscopy. Attainment of equilibrium in the specimen was confirmed by the absence of the change of the concentration of the salt in the solution after the following 24 h incubation at 30 °C.

Table 1 lists the solubility of salts of 2,4,6-trinitrophenol in chloroform and benzene with or without 1 and 2. The salts, which have otherwise very poor solubility, are satisfactorily solubilized in these organic solvents in the presence of 1 and 2. The increase in the solubility is definitely attributable to complex formation of the salts with 1 and 2.

In addition, patent blue (Na salt), methyl orange (Na salt), and sodium 4-nitrophenolate also form complexes with these modified cyclodextrins. In the presence of 2.5 mM (1 M = 1 mol·dm^{-3}) of 2, these salts dissolved in chloroform at 30 °C at the concentrations of 2.4, 2.8×10^{-2}, and 1.2×10^{-2} mM, respectively. In its absence, however, none of them has measurable solubility.

The solubility of the salts in chloroform increased linearly with increase in the concentration of 1 or 2 added in the range involving 0 - 5 mM of 1 or 2. This

result indicates formation of 1 : 1 complex between the salt and 1 or 2.

The cyclic structures are definitely important for 1 and 2 to form complexes with ammonium 2,4,6-trinitrophenolate effectively in chloroform. Neither ethyl acetate nor ethyl carbanilate increases its solubility in chloroform at the concentration of 52.5 (2.5 × 21) mM.[10] The magnitude of the increase of the solubility of calcium 2,4,6-trinitrophenolate by 2.5 mM of 1 is 26 fold larger than that by 52.5 mM of ethyl acetate, whereas the corresponding value by 2.5 mM of 2 is 1.6 fold larger than that by 52.5 mM of ethyl carbanilate. The difference in the solubility increase between 2 and ethyl carbanilate increases with decreasing concentration of the functional group: the magnitude of increase by 0.5 mM of 2 is 3.1 fold larger than that by 10.5 mM of ethyl carbanilate. This result further supports the importance of the cyclic structure of 2.

All the salts of 2,4,6-trinitrophenol exhibited absorption maxima at 346 ± 3 nm on complexation with 1 or 2 in chloroform. These maxima are located at considerably longer wavelength than those (328 ± 2 nm) for the salts dissolved in chloroform with ethyl acetate or ethyl carbanilate, showing that 2,4,6-trinitrophenolate ion and the metal cation are separated from each other to a larger extent in the complexes between the metal salts and 1 or 2.[11] Thus, the complex formation of the salts with 1 or 2 is significantly different from simple solvation of the salts by the solvents.

The magnitude of the complex formation of the salts is highly dependent on the cations, although their organic moieties also have significant effects. In the complex formation of 2,4,6-trinitrophenol, the order in the magnitude is as follows both for 1 and 2 :

$$Ca^{2+} > Li^{+} > Ba^{2+} > Na^{+} > K^{+} > Cs^{+}.$$

Thus, the cations take important roles in the complex formation. In the complex formation of 18-crown-6 with the salts of 2,4,6-trinitrophenol, however, the order was opposite to the one for 1 or 2 : $Li^{+} < Na^{+} < K^{+}$.

In the complexes of 1 and 2, the cations are probably located in the cavity formed by the seven acetyloxy or phenylcarbamoyloxy groups at the C-2 atoms of the glucoses in 1 or 2. According to a CPK molecular model study, the seven acetyloxy groups of 1 can take a conformation in which all the carbonyl groups are directed toward the longitudinal axis of the torus, almost perpendicularly to the axis with the oxygen atoms first. This conformation provides a cavity with a diameter of 1.3-2.0 A, formed by the seven carbonyl oxygen atoms, which can accommodate the metal cations. In the case of 2, either the nitrogen atoms or the carbonyl oxygen atoms in the seven phenylcarbamoyloxy groups at the C-2 atoms provide a cavity.

In addition to 1 and 2, a binarily modified cyclodextrin 3, in which one of the acetyl groups at the secondary hydroxyl groups in 1 is replaced by a benzoyl group,[12] exhibited almost identical activity with 1 for the complex formation with calcium salt of 2,4,6-trinitrophenol both in chloroform and benzene. This result indicates that these types of derivatives of cyclodextrins can be applied to the reactions in organic solvents in a similar way as variously modified cyclodextrins have been successfully used in water, dimethyl sulfoxide, and dimethylformamide.[1,2,13,14]

In conclusion, complex formation of modified cyclodextrins in common organic solvents is shown with the use of 1-3. The cyclodextrin moiety regulates the conformation of ester or carbamoyl groups so that they effectively trap the organic salts. This finding extends the scope of the reactions involving modified cyclodextrins, although the driving force for the complex formation is not necessarily identical with that for the complex formation previously studied.

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