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Difference in Effects of Appended 2-O- and 6-O-Tosyl Groups of β-Cyclodextrin on the Binding and Hydration Reaction of 1-Benzyl-1,4-Dihydronicotinamide

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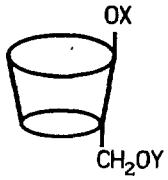
Cyclodextrins (CDs) and their derivatives have attracted great interest as enzyme models because of their ability to form inclusion complexes with great variety of guest molecules from aqueous solution.[1] The tosylated CDs are major intermediates for derivatization of CDs,[2] and show different binding affinity and catalytic effect from parent CDs.[3,4] The stability and structure of the enzyme model/substrate complexes, which are expected to depend on the configuration of the hosts, have large influences on the catalytic effects of the enzyme models.[1] Thus, information on the host structure and the clarification of the structural effects on binding and reactivity of substrates are important for designing enzyme model systems.

Recently, we have shown that the coenzyme NADH analogues, 1,4-dihydronicotinamides, form 1 : 1 inclusion complexes with β-cyclodextrin (β-CD) (**1**) and the acid-catalyzed hydration reaction of the NADH analogues is inhibited by the complexation.[5] We now report the effect of appended tosyl groups of β-CD on the binding and reaction of 1-benzyl-1,4-dihydronicotinamide (BNAH). This gives clear picture about geometry of mono-tosylated β-CD.

Mono(2-O-tosyl)-β-CD, 2-Ts-CD, (**2**) was prepared by reacting β-CD with dibutyltin oxide and then tosyl chloride/triethylamine in dry DMF.[6,7] Mono(6-O-tosyl)-β-CD, 6-Ts-CD, (**3**) was prepared from the reaction between β-CD and tosyl chloride in aqueous NaOH solution.[9]



1; X=H, Y=H
2; X=Tosyl, Y=H
3; X=H, Y=Tosyl

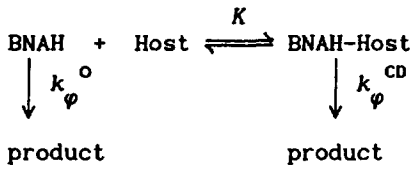
The hydration reaction of BNAH was monitored spectrophotometrically and obeyed pseudo-first-order kinetics with respect to BNAH[5,10] regardless of the presence of the host (**1**)-(**3**). The rate constants k_φ are summarized in Table 1. Values of k_φ vary significantly with hosts. The effects of host on k_φ are explained in terms of different reaction rates for free and host-complexed BNAH as shown in Scheme 1: we assume 1 : 1 complexation (see, below).

K is the binding constant of BNAH with host. The apparent k_φ determined at host concentration [host] is related with K, k_φ^o and k_φ^{CD} by Eqn. (1).[5]

Table 1. Kinetics and Binding Constants of 1-Benzyl-1,4-dihydronicotinamide in 2% DMSO-98% H_2O (v/v) of Ionic Strength 0.1 M at 25℃[a]

Host	$k\varphi^a/10^{-4}s^{-1}$	$K^c/dm^3\ mol^{-1}$	
		kinetic	fluorescence
without host	5.1	–	–
(1), β-CD	2.5	1040	1000
(2), 2-Ts-CD	3.1	650	650
(3), 6-Ts-CD	4.2	210	–[b]

[a]Pseudo-first-order rate constants for hydration reaction of BNAH at pH 5.0 (adjusted with 0.01 M cacodylate buffer) in 1.0 mM host solutions: $[BNAH]_o=0.1$ mM. [b]Solubility[8] of 6-Ts-CD is too low to determine the binding constant by spectroscopic method. [c]Relative Uncertainty of K values is ±10% (Ref. 5).



Scheme 1.

$$(1-k_\varphi/k_\varphi^o)^{-1}=(1-k_\varphi^{CD}/k_\varphi^o)^{-1}+\{(1-k_\varphi^{CD}/k_\varphi^o)K\}^{-1}[host]^{-1} \quad (1)$$

We calculated K values from data in Table 1 under the assumption that β-CD-complexed BNAH molecules are virtually unreactive, *i.e.*, $k_\varphi^{CD}\cong 0$.[5] The results are included in Table 1.

Fluorescence titration of BNAH with host gives the value of binding constant.[5] Figure 1 shows the plots of the titration data for BNAH binding with β-CD and 2-Ts-CD according to Benesi-Hildebrand-type equation [Eqn. (2)].[5,11]

$$\Delta I_F/[host]=K(\Delta I_F^{CD})-K\Delta I_F \quad (2)$$

Good linearities ($r>0.997$) clearly indicate that BNAH forms 1 : 1 complexes with 2-Ts-CD as well as with β-CD. The binding constants determined by this method (Table 1) agree well with the corresponding values from kinetic data. Also, it is found that the enhancement in emission intensity of BNAH upon binding with the hosts, 2.6±0.1, is same for both hosts.

The binding constants of BNAH to the hosts are in the order 6-Ts-CD<2-Ts-CD<β-CD. Since 1-benzyl moiety of BNAH protrudes outside from the cavity of β-CD,[5] inclusion of tosyl group into the cavity would be expected to lead weaker binding of BNAH, which should be the case with 6-Ts-CD.[12] Structurally, the toluene ring of 2-Ts-CD cannot insert into cavity. In this aspect, the weaker binding of BNAH with 2-Ts-CD, compared to that with β-CD, is rather unexpected: β-CD capped with aromatic group and difunctionalized β-CD with *o*-carboxyphenylthio and 1-pyrrolidinyl groups form stronger complexes with 1-anilino-8-naphthalenesulfonate[3] and tryptophan,[13] respectively, presumably by hydrophobic interaction. The weaker binding between BNAH and 2-Ts-CD could be attributed to steric interaction between

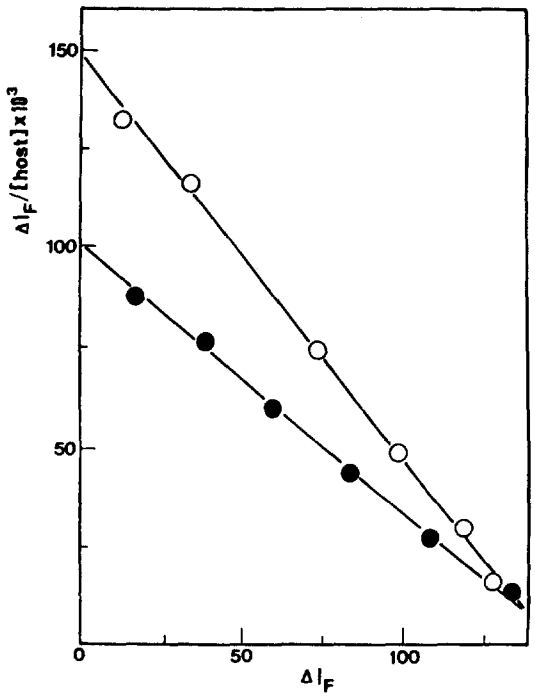


Figure 1. Benesi-Hildebrand plots [Eqn. (2)] of BNAH/β-CD (○) and BNAH/2-Ts-CD (●) complexation at 25℃. The data were obtained from pH 9.0 0.01 M borate buffer and taken at 463 nm. $\lambda_{ex}=350$ nm.

protruding benzyl group of BNAH and tosyl group of 2-Ts-CD, which may overwhelm the hydrophobic interaction. This is supported by the facts that the glucose unit of β-CD is in the *C*1 conformation, and the secondary hydroxyl groups are equatorial, and then the tosyl moiety of 2-Ts-CD should be also equatorial,[14] *i.e.*, located directly over the cavity. This work demonstrates that there are large differences in the structure and binding affinity of mono-tosylated β-CDs depending on the position of the substituent. It will be of interest to see how the structural effect varies with guest molecules, and with other functional groups.

Acknowledgement. This work was supported by grants from the Korea Science and Engineering Foundation through Center for Biofunctional Molecules and grant number 91-03-00-03.

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12. Inclusion of the toluene group does not necessarily result in weaker binding of guests. When the guest is large and only partially included into the cavity, the hydrophobic interaction between the toluene group and the inserted portion of the guest molecule would lead stronger binding. This seems to be the case with ferrocene-monoacrylate which exhibits large binding constant with 6-Ts-CD than with β-CD, while ferrocene-diacrylates show the reverse trend.[4].
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Synthesis of 2-Methylbenzo[*b*]Furan Derivatives from Aryl β-Chloroallyl Ethers with Aluminium Chloride

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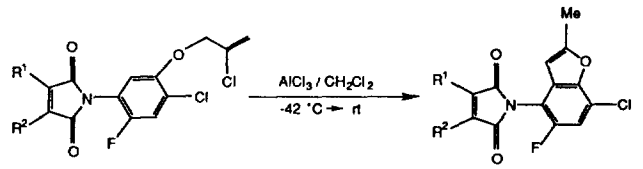
Although there are several synthetic methods of benzofuran derivatives,[1] they are often hampered by low yields or involve starting materials which are not easily accessible. One possible method for these compounds involves the use of Claisen rearrangement of aryl β-chloroallyl ethers[2] or aryl propargyl ethers.[3] However, these methods have some limitations. In the case of aryl β-chloroallyl ethers, the use of solvents that have high boiling point with long reaction time is required and resulted in low yields of products in most cases.[2] Claisen rearrangement of aryl propargyl ethers needed electron withdrawing substituents on the aryl group to afford the desired benzofuran derivatives in reasonable yields. Otherwise, benzopyran derivatives or a mixture of products were obtained.[3]

In our synthetic studies on the herbicidal maleimide derivatives[4] such as **3** and **4** by the use of Claisen rearrangement, we found that treatment of **1** or **2** with $AlCl_3$ at low temperature (−42℃→*rt*) afforded the desired 2-methylbenzo[*b*]furan derivatives in good yields *via* tandem Claisen rearrangement-cyclization reaction. Aluminium chloride afforded the best results for the formation of **3** and **4** in comparison with the other catalysts such as Et_2AlCl, $SnCl_4$, or CF_3COOH. Various Lewis acids including $AlCl_3$ or Bronsted acids have been used in Claisen rearrangement.[5] However, to our knowledge, there were no reports on the reaction of aryl β-chloroallyl ethers with $AlCl_3$.

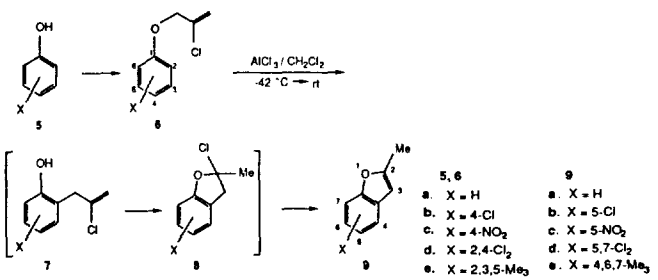
Table 1. Synthesis of 2-Methylbenzo[*b*]Furan Derivatives

Entry	Starting material	Condition	Product	Yield (%)
1	**1**	−42℃→*rt*	**3**	72
2	**1**	*rt*	**3**	47
3	**2**	−42℃→*rt*	**4**	69
4	**2**	*rt*	**4**	59
5	**6a**	−42℃→*rt*	**9a**	36
6	**6b**	−42℃→*rt*	**9b**	75
7	**6c**	−42℃→*rt*	**9c**	45
8	**6d**	−42℃→*rt*	**9d**	63
9	**6d**	*rt*	**9d**	40
10	**6e**	−42℃→*rt*	**9e**	38

Thus, we examined the reactions with some aryl β-chloroallyl ethers **6**. Aryl β-chloroallyl ether derivatives **6** were readily prepared by treatment of the corresponding phenol derivatives **5** with 2,3-dichloropropene and potassium carbonate in acetone heated under reflux. The ether **6** were dissolved in dry dichloromethane and cooled to −42℃ (dry ice in CH_3CN). Anhydrous $AlCl_3$(1 equiv.) was added in one portion and stirred for 2 h. Then the reaction mixture was slowly warmed to room temperature and stirred for 2 h.



The reaction mixture was poured into cold water and extracted with dichloromethane. After usual work-up the crude products were purified by column chromatography to afford the desired compounds **9** in moderate yields. These results were summarized in Table 1.



As shown in Table 1, the reactions at room temperature (entry 2, 4, and 9) showed lower yields than the reactions performed at low temperature. The use of 1.0 equiv. of $AlCl_3$ was needed to obtain the optimal results. The sequence of