Tetrahedron Letters Vol. 21, pp 1541 - 1544

0040-4039/80/0415-1541$02.00/0

SELECTIVITY VARIATION IN HYDROLYSIS OF PHENYL ACETATES BY SIMPLE MODIFICATIONS OF β-CYCLODEXTRIN.

Kahee Fujita*, Akihiro Shinoda and Taiji Imoto

Faculty of Pharmaceutical Sciences, Kyushu University

Maidashi, Higashiku, Fukuoka 812, Japan.

By reaction of β-cyclodextrin 6-monotosylate with alkyl mercaptans, 6-deoxy-6-alkylthio-β-cyclodextrins, 2, 3, and 4, were prepared. Studies of the hydrolyses of m- and p-substituted phenyl acetates showed that the well-known meta-selectivity effect occurred with 2, while none was observed with 4. This variation in selectivity was due to a change in the catalytic rate constant caused by the substituent on β-cyclodextrin.

In the past decade, many catalytic processes modeling enzymic reactions have been extensively studied by use of α- or β-cyclodextrins[1]. Introduction of an appropriate catalytic group to the cyclodextrin has been successfully carried out to obtained a rather sophisticated model of an enzyme[2]. Also, a dramatic enhancement of the inclusion ability of the cyclodextrin was attained by the capping of the cavity with an hydrophobic moiety[3] or a metal complex[4].

In the studies of the hydrolyses of substituted phenyl acetates by α- or β-cyclodextrins, meta-substituted phenyl esters were more rapidly hydrolyzed than the corresponding para-isomers, a phenomenon termed "meta-selectivity"[1b]. This selectivity is apparently dependent on the depth of the cavity of the cyclodextrin and should be altered by appropriate modifications of the cyclodextrins. In our previous paper[5], we demonstrated the reversion from "meta-selectivity" to "para-selectivity" by a complete capping of β-cyclodextrin: complete capping (1) decreased the maximum catalytic rate constant (k_c) for the para-esters to values quite similar to those for the corresponding meta-isomers. Also, binding of the para-esters was enhanced to much greater degree.

In this paper, we wish to demonstrate that simpler modifications of β-cyclodextrin also change the selectivity for ester hydrolyses because a different mechanism come into play.

Modifications of β-cyclodextrin (2, 3 and 4) were carried out by the reaction of mercaptans and β-cyclodextrin 6-monotosylate, 5[6]. The modified cyclodextrins were purified by repeated

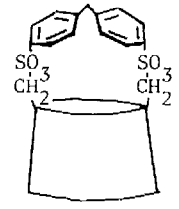
Table I. Maximum Catalytic Rate Constants (k_c) and Dissociation Constants (K_d) for Reactions of Modified β-Cyclodextrins with m- and p-Substituted Phenyl Acetates[a].

AcO-C_6H_4-X	k_c (x 10^{-3} sec^{-1})			K_d (x 10^{-3} M)		
X	2	3	4	2	3	4
p-NO_2	90±14	106±1	136±3	5.1±0.9	1.83±0.03	0.73±0.03
m-NO_2	521±117	342±32	150±5	6.2±1.6	3.1±0.2	0.76±0.04
p-Me	4.91±0.48	10.8±2.3	24.4±1.8	2.1±0.3	1.5±0.5	1.00±0.12
m-Me	18.5±2.4	19.8±0.4	21.1±1.8	4.4±0.7	2.62±0.06	0.73±0.12

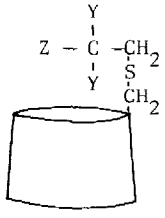
[a] In pH 10.60 (I=0.15) $NaHCO_3$-Na_2CO_3 buffer, 25°C, with 0.50-0.70% (v/v) CH_3CN added.

Table II. Selectivity in Reactions of Modified β-Cyclodextrins with m- and p-Substituted Phenyl Acetates (25°C. pH 10.60, I=0.15).

AcO-C_6H_4-X	k_c/K_d ($M^{-1}\cdot sec^{-1}$)			$(k_c/K_d)_{para}/(k_c/K_d)_{meta}$		
X	2	3	4	2	3	4
p-NO_2	17.9	58.1	187	0.213	0.520	0.940
m-NO_2	83.9	111.7	199			
p-Me	2.35	7.11	24.4	0.564	0.940	0.841
m-Me	4.17	7.56	29.0			



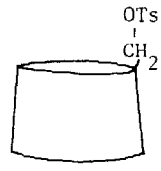
1



2, Y=H, Z=OH

3, Y=H, Z=CH_3

4, Y=Z=CH_3



5

recrystallization from water and characterized by IR, NMR, FD mass spectrometry, and elemental analyses[7]. The hydrolyses (pH 10.60) of meta- and para-nitro- and methyl-phenyl acetates were measured spectroscopically at 25° in the presence of an excess of the modified or native β-cyclodextrins and showed pseudo-first-order kinetics[8]. From the Eadie treatment of the kinetic data[8], the dissociation constants (K_d) and the maximum catalytic rate constants (k_c) were obtained (Table I and Scheme I).

As the hydrophobic nature of the substituent of the cyclodextrin increased from 2 to 4, the following results were obtained; (1) the selectivity factor, (k_c/K_d) increased (Table II), (2) the ratio of the selectivity factor, $(k_c/K_d)_{para}/(k_c/K_d)_{meta}$, increased up to almost unity, (3) all values of K_d decreased, (4) the K_d value for the meta-ester was always similar to that for the corresponding para-ester, and (5) the value of k_c for the para-esters increased while that for the meta-esters decreased or increased only slightly. While the well-known "meta-selectivity" effect was highly conspicuous with 2, essentially no selectivity was observed with 4. This lack of selectivity with 4 was due primarily to an increase or decrease of k_c values for the para- or meta-esters, respectively.

Thus the well-known "meta-selectivity" effect is not a general property of cyclodextrin catalysis. Instead, selectivity can be easily varied by simple modifications of the cyclodextrin structure which in turn leads to changes in k_c and K_d depending on the functional group utilized in the modification.

$$\text{Modified Cyclodextrin} + \text{Phenyl Acetate} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Complex} \xrightarrow{k_c} \text{Acetyl-Modified Cyclodextrin} + \text{Phenolate}$$

$$\text{where } K_d = \frac{k_c + k_2}{k_1}$$

Scheme I

References and Notes

1. For examples; (a) F. Cramer and W. Kampe, J. Amer. Chem. Soc., 87, 1151 (1975). (b) R. L. van Etten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, ibid., 89, 3242 (1967). (c) R. Bleslow and P. Cambell, Bioorg. Chem., 1, 140 (1971). (d) I. Tabushi, K. Fujita, and

H. Kawakubo, J. Amer. Chem. Soc., 99, 6456 (1977). (e) I. Tabushi, Y. Kuroda, K. Fujita, and H. Kawakubo, Tetrahedron Lett., 2083 (1978). (f) I. Tabushi, K. Yamamura, K. Fujita, and H. Kawakubo, J. Amer. Chem. Soc., 101, 1019 (1979).

2. For examples; (a) F. Cramer and G. Mackensen, Angew. Chem., 78, 641 (1966). (b) R. Breslow and L. E. Overmann, J. Amer. Chem. Soc., 92, 1075 (1970). (c) W. B. Gruhn and M. L. Bender, Bioorg. Chem., 4, 219 (1975).

3. (a) J. Emert and R. Breslow, J. Amer. Chem. Soc., 97, 670 (1975). (b) I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata, and K. Fujita, ibid., 98, 7855 (1977). (c) I. Tabushi, K. Shimokawa, and K. Fujita, Tetrahedron Lett., 1527 (1977). (d) I. Tabushi, L. C. Yuan, and K. Fujita, ibid., 2507 (1977).

4. I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, and K. Yamamura, J. Amer. Chem. Soc., 99, 7100 (1977).

5. K. Fujita, A. Shinoda, and T. Imoto, J. Amer. Chem. Soc., 102, in press (1980).

6. The procedure of the present modification was similar to that described elsewhere. See ref.(3c).

7. Molecular weights of 2, 3, and 4 were determined by means of the field desorption mass spectra which will be reported in near future. 2: Found: C, 40.76, H, 6.49. Calcd for $C_{44}H_{74}O_{35}\cdot 6H_2O$: C, 40.55, H, 6.65. ^{1}H-NMR (D_2O): δ2.62 (2H, $S\underline{CH_2}CH_2OH$), 2.9 (2H, cyclodextrin-$\underline{CH_2}S$), 4.90 (7H, C_1H of cyclodextrin) and 3.2-4.1 (42H, $SCH_2\underline{CH_2}OH$ and cyclodextrin protons other than C_1H). 3: Found: C, 44.61, H, 6.46. Calcd for $C_{45}H_{76}O_{34}S\cdot H_2O$: C, 44.63, H, 6.49. ^{1}H-NMR (D_2O): δ0.83 (3H, $CH_2CH_2\underline{CH_3}$), 1.45 (2H, $CH_2\underline{CH_2}CH_3$), 2.46 (2H, $\underline{CH_2}C_2H_5$), 2.9 (2H, cyclodextrin-$\underline{CH_2}S$), 4.90 (7H, C_1H of cyclodextrin), and 3.2-4.1 (40H, cyclodextrin protons other than C_1H). 4: Found: C, 45.58, H, 6.59. Calcd for $C_{47}H_{80}O_{34}S\cdot H_2O$: C, 45.55, H, 6.67. ^{1}H-NMR (D_2O-DMSO-d_6): δ0.80 (9H, CMe_3), 2.66 (2H, $S\underline{CH_2}CMe_3$), 2.9 (2H,cyclodextrin-$\underline{CH_2}S$), 4.84 (7H, C_1H of cyclodextrin), and 3.2-4.1 (40H, cyclodextrin protons other than C_1H). Ir spectra of 2, 3 and 4 were very similar to that of β-cyclodextrin.

8. Measurement and treatment of the kinetic data were carried out as described elsewhere. See ref. (1b).

(Received in Japan 25 January 1980)