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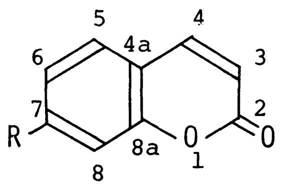
# MODIFICATION OF SUBSTITUENT EFFECT BY CYCLODEXTRIN COMPLEXATION IN ALKALINE HYDROLYSIS OF 7-SUBSTITUTED COUMARINS

Kaneto UEKAMA, Chien-Li LIN, Fumitoshi HIRAYAMA, Masaki OTAGIRI,
Akira TAKADATE, and Shujiro GOYA

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi,
Kumamoto 862

The substituent effect in the alkaline hydrolysis of 7-substituted coumarins in the absence and presence of cyclodextrin (CyD) was analyzed by a modified Hammett equation (1). It was shown that the transmission route of the substituent effect to reaction site was altered by the inclusion of coumarin molecule within hydrophobic CyD cavity.

Although cyclodextrin (CyD) is known to influence various kind of reactions,$^{1-4)}$ the catalytic behavior of CyD in fused ring system is not well investigated.$^{5)}$ In our preliminary study, it was found that the hydrolysis rate of 7-substituted coumarins was significantly influenced by CyD. To elucidate the substituent effects in fused ring system, the data can be pertinently analyzed using two parameter equation rather than the single parameter $\sigma$ scale. For the reactivity of 7-substituted coumarins in which the reacting center (C-2) is attached to the substituted benzene ring in two places (C-4a and C-8a), the Hammett equation may be applicable in form,$^{6)}$



R: H, $NO_2$, Br, Cl, $CH_3$, $CH_3O$, $NH_2$

$$\log k_{obs} = \rho_m \cdot \sigma_m + \rho_p \cdot \sigma_p + \log k_o \qquad (1)$$

where $\sigma_m$ and $\sigma_p$ refer to the substitution constants of R for the position (meta and para) relative to the points of attachments of C-8a and C-4a of the side chain, respectively. This equation permits the estimation of the relative importance of two alternate paths in transmission of electronic effects of substituents to the reaction site.7) Thus, the present study deals with an adequate test of equation (1) to examine the reactivity changes of 7-substituted coumarins in the presence of three CyDs (α-, β-, and γ-CyDs).

The hydrolysis of 7-substituted coumarins ($4.0 \times 10^{-5}$ M) in the absence and in the presence of CyD($1.0 \times 10^{-2}$ M) was followed spectrophotometrically8,9) by measuring the decrease in absorbance of coumarins (analytical wavelength is listed in Table I), in pH 11.2 phosphate buffer ($\mu = 0.2$) at 40°. The apparent first-order rate constants ($k_{obs}$) are summarized in Table I. The $k_{obs}$ values of CyD systems can be assumed to be equal to the rate constants of complexed coumarins,10) since the concentration of CyD was largely in excess compared to that of coumarins under these experimental conditions.

As shown in Table I, the rate acceleration for the compounds bearing electron withdrawing group and rate deceleration for the compounds bearing electron donating group were observed in the cases of α- and β-CyD systems. On the other hand, the deceleration of hydrolysis rate was observed for γ-CyD system, indicating that the reaction center of the coumarins may be completely included within γ-CyD cavity. Then, the data in Table I were analyzed by equation (1), using the method of multiple regression. As shown in Table II, good correlations were found in seven series of reactions, where $\sigma_m$ and $\sigma_p$ highly correlated with correlation coefficient $r > 0.9$. This indicates that $\sigma_m$ and $\sigma_p$ are not independent and that two pahts through C-4a and C-8a may be involved in the transmission of electronic effect of 7-substituent to the reaction site. In the absence of CyD in aqueous solution, the substituent effect of 7-substituted coumarins appeared to be predominantly transmitted through C-4a rather than C-8a, even though the latter route is fewer bonds away from the C-7 position. This may be due to the lesser resonance interaction between C-2 and C-7 through C-8a.11) In the presence of CyD, however, the transmission of the electronic effect through C-8a was found to become predominant in the order of α- > β- > γ-CyD. This indicates that the coumarin molecule may be favorably included in α-CyD cavity to transmit the substituent effect from C-7 to C-2 through C-8a. The preliminary $^1$H-NMR study12) revealed that the benzene ring of coumarin was located at entrance of α-CyD cavity, it could be penetrate further into β-CyD, and was most loosely bonded by γ-CyD. Moreover, the extent of hydrophobicity of CyD cavity seems to be responsible for the magnitude of reaction constants, since the smaller the cavity size (α- < β- < γ-CyD), the lesser the

Table I. Hydrolysis Rates ($k_{obs}$, x 10 $min^{-1}$)[a] of 7-Substituted Coumarins[b] at pH 11.2, 40°

| Substituent | Without additives[c] | CyD system[d] | | | Mixed solvent system[e] | | | Analytical Wavelength (nm) |
|---|---|---|---|---|---|---|---|---|
| | | α-CyD | β-CyD | γ-CyD | 75 v/v% EtOH | 50 v/v% dioxane | 75 v/v% dioxane | |
| H | 1.73 | 1.68 | 1.50 | 1.34 | 0.886 | 0.675 | 0.260 | 278 |
| $NO_2$ | 28.2 | 45.5 | 37.2 | 24.5 | 12.9 | 17.9 | 7.28 | 420 |
| Br | 4.72 | 17.7 | 7.46 | 4.19 | 5.07 | 2.71 | 1.14 | 290 |
| Cl | 4.43 | 10.4 | 6.22 | 3.64 | 4.09 | 2.17 | 0.876 | 290 |
| $CH_3$ | 1.05 | 1.22 | 1.01 | 0.835 | 0.535 | 0.391 | 0.170 | 290 |
| $CH_3O$ | 0.824 | 0.950 | 0.848 | 0.719 | 0.390 | 0.284 | 0.110 | 330 |
| $NH_2$ | 0.444 | 0.423 | 0.417 | 0.341 | 0.212 | 0.184 | 0.0852 | 350 |

a) Accuracy of ± 3 %: The $k_{obs}$ values for CyD systems could be taken as the rate constants of complexes, because they were identical with those in the presence of 5 x $10^{-3}$ M CyD within experimental errors. b) 4.0 x $10^{-5}$ M. c) In phosphate buffer ($\mu$= 0.2). d) In the presence of 1.0 x $10^{-2}$ M CyD in phosphate buffer ($\mu$= 0.2). e) The pH of the reaction solution was adjusted with appropriate NaOH solution.

Table II. Test of Equation (1)[a] for Hydrolysis Rate of 7-Substituted Coumarins

| System | $\rho_m$[b] | $\rho_p$[c] | r[d] | n[e] | log $k_o$[f] |
|---|---|---|---|---|---|
| alone | 0.557 | 0.949 | 0.990 | 7 | -0.763 |
| α-CyD | 1.28 | 0.772 | 0.975 | 7 | -0.721 |
| β-CyD | 1.02 | 0.809 | 0.991 | 7 | -0.796 |
| γ-CyD | 0.695 | 0.894 | 0.992 | 7 | -0.872 |
| 75 v/v% EtOH | 0.818 | 0.883 | 0.975 | 7 | -1.04 |
| 50 v/v% dioxane | 0.850 | 0.938 | 0.982 | 7 | -1.17 |
| 75 v/v% dioxane | 0.891 | 0.885 | 0.976 | 7 | -1.56 |

a) For the calculation, Hammett substituent constants ($\sigma_m$, $\sigma_p$) were used.
b) Transmission through C-8a. c) Transmission through C-4a.
d) Multiple correlation coefficient. e) The number of compounds involved in the series. f) The intercept of the regression plane and the log k axis.

water content is expected. In fact, the substituent effect was magnified by the addition of organic solvents, where the lesser polar the solvent, the larger the reaction constant ($\rho_m + \rho_p$) was observed.

Aforementioned results clearly indicate that the electron mobility in coumarin molecule is facilitated in the hydrophobic environments, i.e. microsolvent effect.$^{13)}$ This kind of knowledge will provide not only the elucidation of enzyme mechanism but also improving the chemical reactivity of coumarins by means of inclusion complex formation.

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