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EFFECTS OF α- AND β-CYCLODEXTRINS ON BASE-CATALYZED ISOMERIZATION OF PROSTAGLANDIN A_1 AND PROSTAGLANDIN A_2

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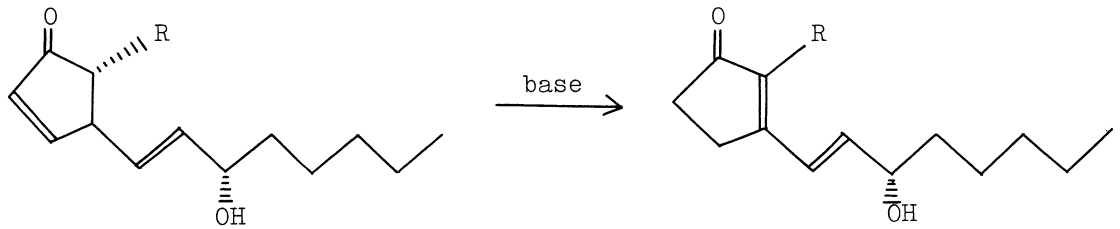
Both α- and β-cyclodextrins (α-CyD, β-CyD) increased the isomerization rates of A-type prostaglandins (prostaglandin A_1 and prostaglandin A_2) in alkaline condition, where acceleration effect of α-CyD was somewhat different from that of β-CyD. Importance of the spacial relationship between host and guest molecules was reflected in kinetically determined formation constants, activation parameters, and thermodynamic parameters for inclusion complex formation.

Since cyclodextrins (CyDs) are known to influence the rate of various kind of organic reactions, these data are particularly useful for discussing ideas about mechanisms of enzymatic reactions.[1-5] We recently reported that the inclusion complexation of some naturally occurring prostaglandins with α- and β-CyDs in aqueous solution.[6,7] The enone moiety of A-type prostaglandins (PGAs) is susceptible to isomerization reaction in alkaline condition to form B-type prostaglandins (PGBs).[8]



PGAs PGBs

PGA_1, PGB_1: R = $(CH_2)_6COOH$

PGA_2, PGB_2: R = $CH_2CH{=}CH(CH_2)_3COOH$

In the present study, effects of α- and β-CyDs having different cavity size on base-catalyzed isomerization of PGAs such as prostaglandin A_1 (PGA_1) and prostaglandin A_2 (PGA_2) have been investigated. Isomerization rates of PGAs (3.8×10^{-5} M) in the absence and presence of CyDs (varied from 1.0 to 5.0×10^{-3} M) were followed spectrophotometrically by measuring the appearence of PGBs (at 284 nm) at pH 11.9 (0.1 M sodium phosphate buffer, μ=0.2). The first order dependence of the rate constants upon hydroxide ion concentration was ascertained for PGAs.[9]

As shown in Fig. 1, both α- and β-CyDs significantly enhanced the isomerization rates of PGAs. The CyDs-induced rate changes were quantitatively treated to obtain the formation constant (K_c) and rate constant (k_c) of 1:1 inclusion complexes, based on the following scheme,[10,11]

$$\begin{array}{ccccc} \text{PGAs} & + & \text{CyDs} & \overset{K_c}{\rightleftharpoons} & \text{PGAs-CyDs} \\ \Big\downarrow k_o & & & & \Big\downarrow k_c \\ \text{PGBs} & & & & \text{PGBs} + \text{CyDs} \end{array}$$

$$\frac{(\text{CyDs})_t}{k_{obs} - k_o} = \frac{1}{k_c - k_o} \cdot (\text{CyDs})_t + \frac{1}{K_c \cdot (k_c - k_o)} \qquad \text{(Eq. 1)}$$

where k_o and k_{obs} are apparent first order rate constants in the absence and presence of CyDs, respectively, and $(\text{CyDs})_t$ is total concentration of CyDs. Activation and thermodynamic parameters were obtained from the temperature studies of k_o, k_c, and K_c. The Arrhenius and van't Hoff plots fell fairly on the straight line over temperature range between 35 and 60° with accuracy of 5 %.

Table I summarizes the kinetics and thermodynamic data for PGAs-CyDs systems. The differences between rate-acceleration effects of α- and β-CyDs are associated with a little difference in enthalpy of activation (ΔH^*), but with a large difference in entropy of activation (ΔS^*). The apparent absence of ΔH^* difference may result from a masking of CyDs-mediated decrease in ΔH^* by an endothermic conformation change of the guest molecule.[12] Marked differences between thermodynamic parameters (ΔH, ΔS) for complex formation of α-CyD system and those of β-CyD system were also noted.

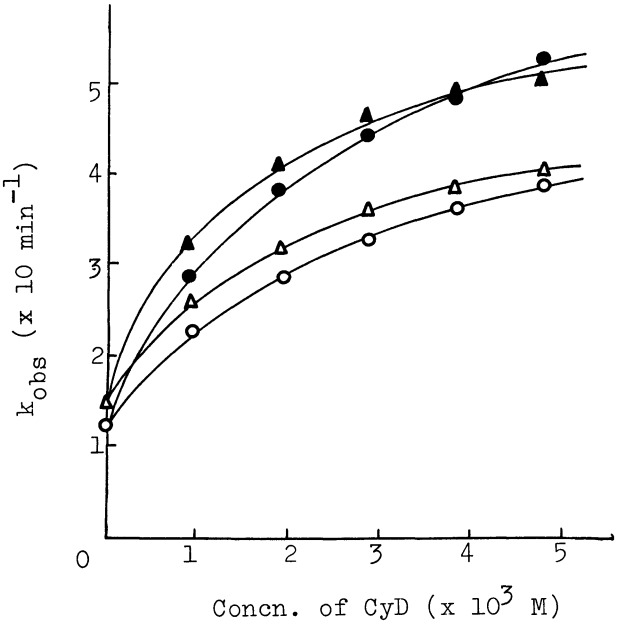


Fig. 1. The plots of observed rate constants for isomerization of PGAs vs. cyclodextrin concentration in phosphate buffer (pH = 11.9, μ = 0.2) at 60°.

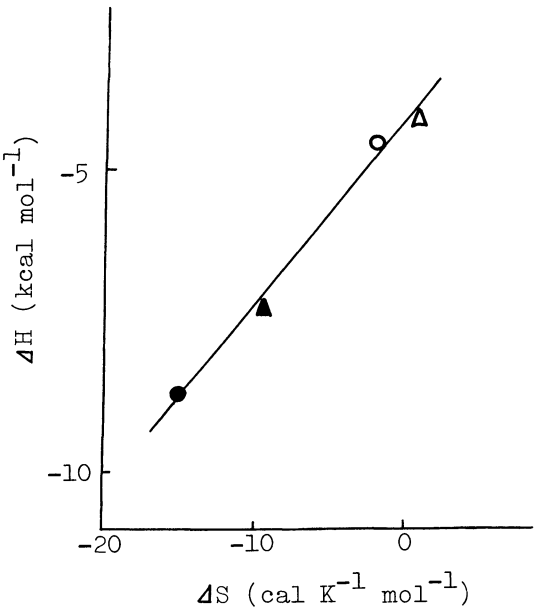


Fig. 2. The plots of ΔH vs. ΔS for complex formation of PGAs with CyDs.

o: PGA_1—α-CyD, ●: PGA_1—β-CyD, Δ: PGA_2—α-CyD, ▲: PGA_2—β-CyD

Table I. Kinetics and Thermodynamic Data of PGAs-CyDs Systems at 60°

System	Rate constant and Activation parameter				Formation constant and Thermodynamic parameter		
	k_o / min^{-1}	k_c / min^{-1}	ΔH^* / kcal/mol	ΔS^* / cal/(K mol)	K_c / M^{-1}	ΔH / kcal/mol	ΔS / cal/(K mol)
PGA_1	0.124		17.4	-18.7			
PGA_1—α-CyD		0.567	14.6	-24.1	320	-4.6	-2.3
PGA_1—β-CyD		0.770	16.7	-17.1	360	-8.8	-15
PGA_2	0.141		17.6	-17.8			
PGA_2—α-CyD		0.514	15.0	-23.3	480	-4.2	0.5
PGA_2—β-CyD		0.604	16.8	-17.3	600	-7.4	-9.4

Inclusion complexation seems to be predominantly due to favorable enthalpy change and entropy change contradictorily contributes, in general. In fact, a linear relationship between ΔH and ΔS was obtained with a compensation temperature[13] of 319 ^{o}K (Fig. 2).

In sharp contrast α-CyD system showed small K_c values, the smaller cavity apparently allowing little penetration of the guest molecule, particularly for PGA_1 having floppy side chains.[8] Above results as well as circular dichroism and ^{13}C-NMR studies[7,14] further suggested that binding of prostaglandins to α-CyD is somewhat different from that of β-CyD.

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