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IMPROVING THE AQUEOUS STABILITY OF PROSTAGLANDIN E_2 AND PROSTAGLANDIN A_2 BY INCLUSION COMPLEXATION WITH METHYLATED-β-CYCLODEXTRINS

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The effects of two methylated-β-cyclodextrins, heptakis(2,6-di-O-methyl)-β-cyclodextrin (DM-β-CyD) and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (TM-β-CyD), on the dehydration rate of prostaglandin E_2 (PGE_2) and the isomerization rate of prostaglandin A_2 (PGA_2) in aqueous alkaline solution were investigated in comparison with natural β-cyclodextrin (β-CyD). In contrast to the acceleration effect of β-CyD, both DM-β-CyD and TM-β-CyD significantly retarded the reaction rates. The stabilizing effect of DM-β-CyD was larger than that of TM-β-CyD. Stability constants and rate constants of the complexes were kinetically determined on the basis of 1:1 inclusion complex formation. The data suggest that DM-β-CyD is useful in the stabilization of PGEs and PGAs in aqueous solution.

KEYWORDS —— prostaglandin E_2 dehydration; prostaglandin A_2 isomerization; methylated-β-cyclodextrin; inclusion complexation; stabilization

Prostaglandins are essentially long-chain fatty acids containing a substituted cyclopentane ring. The β-hydroxyketo moiety in E-type prostaglandins (PGEs: PGE_1 and PGE_2) is extremely susceptible to dehydration under acidic or alkaline conditions, giving A-type prostaglandins (PGAs: PGA_1 and PGA_2) which are consecutively isomerized to B-type prostaglandins (PGBs: PGB_1 and PGB_2) under alkaline conditions.1) This chemical instability of PGEs has limited the development of dosage formulas, a substantial challenge to pharmaceutical scientists.2) We have recently reported3) that the chemical stability of PGE_1 in solid state was significantly improved by cyclodextrin (CyDs) complexations. However, an attempt to stabilize PGE_1 or PGA_1 in aqueous solution was rather disappointing because the natural CyDs had positive-catalytic effects on the reactions.4)

Recently, considerable attention has been paid to chemically modified CyDs since their physicochemical properties and inclusion behaviors are significantly different from those of natural CyDs.5) In the present study, we successfully stabilized PGE_2 and PGA_2 in aqueous solution, which are known to be much more unstable than PGE_1 and PGA_1,[1)] by using two methylated-β-CyDs, i.e., heptakis(2,6-di-O-methyl)-β-CyD (DM-β-CyD) and heptakis(2,3,6-tri-O-methyl)-β-CyD (TM-β-CyD).

The consecutive reaction rate of PGE_2 (see Chart 1, dehydration (k_1) and isomerization (k_2)) was spectrophotometrically monitored by measuring the increased absorbance of PGB_2 at 284 nm.[1)] The graphically calculated k_1 and k_2 values from the PGB_2 concentration-time curves were refined to obtain the best fit by using a nonlinear least-squares method for a consecutive-first order reaction.

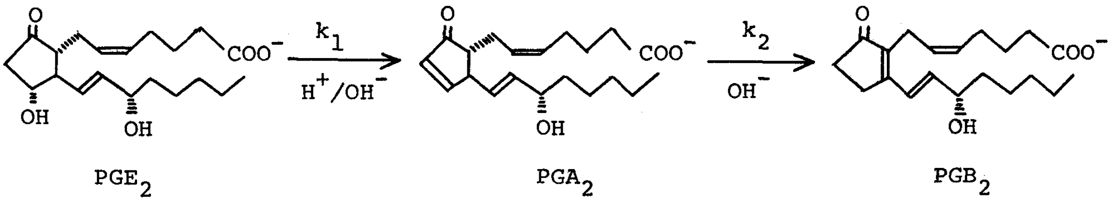

Chart 1

Figure 1 shows the effects of DM-β-CyD, TM-β-CyD and β-CyD concentrations on the reaction rates of PGE_2 and PGA_2. In contrast to β-CyD, both DM-β-CyD and TM-β-CyD were found to retard the reaction rates with increasing concentrations. The dependency of k_{obs} on the CyD concentration was quantitatively treated by Eq.(1)[6)] to obtain the stability constant (K_c) and rate constant (k_c) of the complex, on the following 1:1 complexation scheme (Chart 2), where k_o and $(CyD)_t$ are the rate constant in the absence of CyDs and the total concentration of CyDs, respectively.

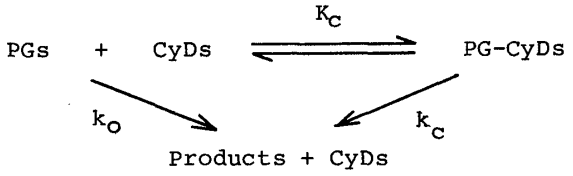

Chart 2

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

The plots according to Eq.(1) fell well on the straight line with an accuracy of 5%. Table I summarizes k_o, k_c, k_c/k_o, and K_c values. As is apparent from Table I, the dehydration and isomerization rates were significantly retarded by the complexations with the methylated CyDs, particularly by the binding to DM-β-CyD. Interestingly, the stabilizing effect of DM-β-CyD was

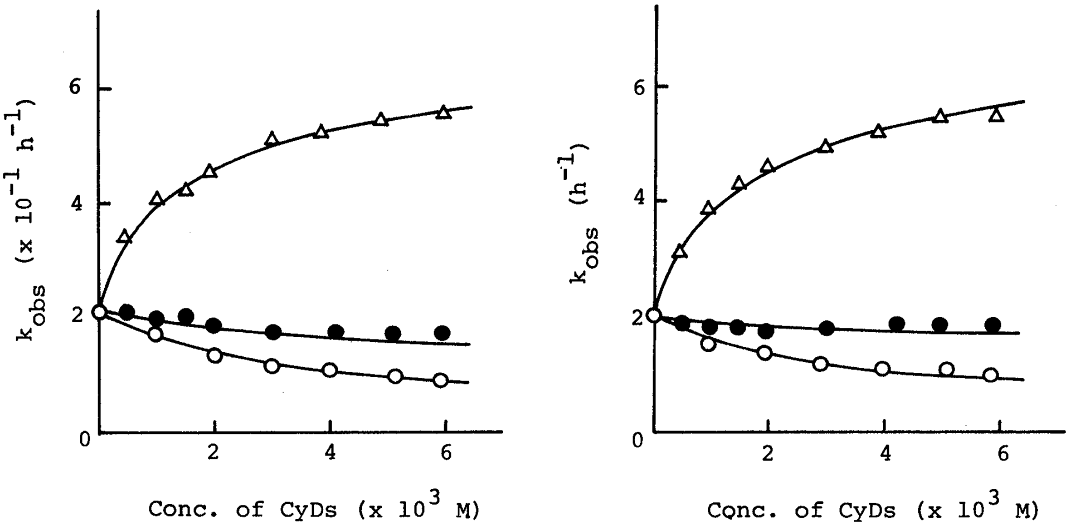

Fig. 1. Effects of Three CyDs on the Rate Constants for Dehydration of PGE_2 (Left) and Isomerization of PGA_2 (Right) in Phosphate Buffer (pH 11.0, μ= 0.2) at 60°C

The concentration of PGE_2 and PGA_2 was 3.0×10^{-5} M.
○: DM-β-CyD, ●: TM-β-CyD, Δ: β-CyD.

Table I. Rate Constants and Stability Constants[a)] of PGE_2-CyD and PGA_2-CyD Systems

System	k_o (h^{-1})	k_c (h^{-1})	k_c/k_o	K_c (M^{-1})
PGE_2	20.8	—	—	—
PGE_2-DM-β-CyD	—	6.93	0.33	620
PGE_2-TM-β-CyD	—	14.7	0.71	280
PGE_2-β-CyD	—	62.0	3.0	940
PGA_2	2.02	—	—	—
PGA_2-DM-β-CyD	—	0.75	0.37	390
PGA_2-TM-β-CyD[b)]	—	—	—	—
PGA_2-β-CyD	—	6.34	3.1	810

a) Kinetic conditions were the same as in Fig. 1.
b) Could not be determined with accuracy due to the small change in k_{obs}.

larger than that of TM-β-CyD. This might be due to little penetration of the bulky guest molecule into the TM-β-CyD cavity since the macrocyclic ring of TM-β-CyD is markedly distorted from the regular heptagonal symmetry of β-CyD and DM-β-CyD.[7] Further studies are now in progress to elucidate the stabilization mechanisms of DM-β-CyD and TM-β-CyD.

Although various attempts have been made to improve the chemical stability of PGEs by pharmaceutical additives, only a few have succeeded in stabilizing them in aqueous solution.[2] So, our present findings will not only provide a useful means for the aqueous preparation of PGEs, they will be also extended to various dosage formulas for other chemically unstable drug molecules, by utilizing the inclusion complexation of methylated CyDs.

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