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Micellar Effects on Base-Catalyzed Isomerization of Prostaglandin A_1 and Prostaglandin A_2

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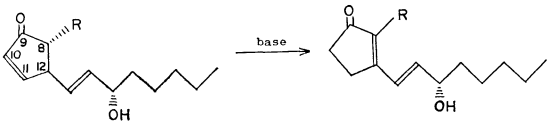
Synopsis. Micellar effects on base-catalyzed isomerization of A-type prostaglandins to B-type prostaglandins were studied. Cationic and non-ionic micellar systems increased the rate of isomerization, but anionic systems either decreased or had negligible effects on the rate constants. Incorporation of the prostaglandins into the hydrophobic interior of the micelles was suggested by circular dichroism spectra.

The enone moiety of A-type prostaglandins (PGA) is susceptible to isomerization in alkaline conditions to form B-type prostaglandins (PGB),[1] which consequently elicites the loss of biological activity.[2] It is well known that micellar systems influence the rate of various kinds of organic reactions, providing useful information about the reaction mechanism.[3] Thus, micellar effects on base-catalyzed isomerization of prostaglandin A_1 (PGA_1) and prostaglandin A_2 (PGA_2) were examined to better understand the nature of rearrangement reactions through substrate-surfactant interactions. The effect of surfactants on the circular dichroism (CD) spectra of PGA were also investigated, anticipating an incorporation of PGA into the hydrophobic interior of the micelles.



PGAs PGAs

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

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

Experimental

Materials. The prostaglandins used were donated by the Ono Pharmaceutical Co., Ltd. Hexadecyltrimethylammonium chloride (CTAC), dodecyltrimethylammonium chloride (DTAC), sodium hexadecyl sulfate (NaCS), sodium dodecyl sulfate (NaLS), and poly(oxyethylene) dodecyl ether (Brij-35) were commercially obtained and purified using the usual methods.[4] All other materials and solvents were of analytical reagent grade.

Measurements. The CD and UV spectra were measured at 25 °C using a Jasco J-40 AS spectropolarimeter and a Shimadzu spectrophotometer, respectively, in a 0.1 M sodium phosphate buffer solution (pH 6.0). The CD spectra are expressed in terms of molar ellipticity, $[\theta]$. The critical micelle concentration (CMC) of the surfactants was determined spectrophotometrically[5] at 60 °C and at pH 11.2.

Kinetic Studies. The isomerization of PGA (3.8×10^{-5} M) in the presence and in the absence of surfactants was followed spectrophotometrically by measuring the apparence of PGB (284 nm) at 60 °C. The first-order dependence of the rate constants on the hydroxide ion concentration was ascertained for both PGA_1 and PGA_2, for an activation energy of 18.7 kcal/mol at pH 12.0.[6] The pH profile of the logarithm of the rate constant (k_{obsd}) for both PGA_1 and PGA_2 is linear with a slope of 0.75 from pH 9.5 to 12.0. No appreciable change in the slope was observed even in the presence of surfactants.

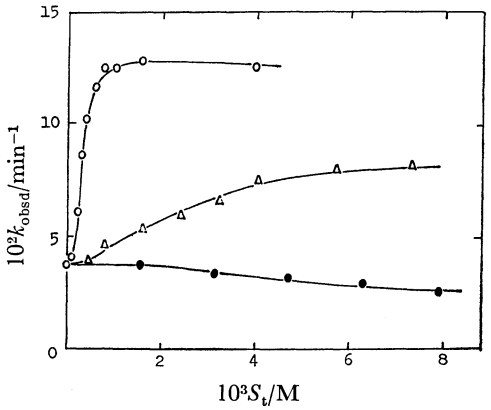


Fig. 1. The plots of observed rate constants for isomerization of PGA_1 *vs.* surfactant concentration, S_t, in phosphate buffer (pH=11.2, μ=0.2) at 60°.
-○-: CTAC, -●-: NaLS, -△-: Brij-35.

Results and Discussion

As is shown in Fig. 1, cationic and non-ionic surfactants enhanced the isomerization rates, but anionic surfactants either decreased or had negligible effects on the rate constants above the CMC values. The results for ionic micellar systems suggest the development of an anionic charge on the cyclopentanone ring of PGA during the rate-determining step. It was also noted that activation of the base (toward C–H proton abstraction) in cationic micelles becames greater with increasing hydrophobic chain length of the surfactant. The observed rate constant (k_{obsd}) as a function of surfactant concentration was quantitatively evaluated[7] to yield the non-micellar (k_o) and micellar (k_m) rates, and the K/N value of the PGA-micelle complex. As is shown in Table 1, the K/N values of the PGA_1 system are larger than those of the PGA_2 system. This may be due to the greater hydrophobic tendency of PGA_1 compared to PGA_2, as is expected from their partition coefficients.[8]

Figure 2 shows the CD spectra of the PGA_1–CTAC system, as an example, where PGA_1 exhibits a strong positive band at 238 nm ($[\theta]=6.10\times10^4$) and a weak negative band at 314 nm ($[\theta]=-9.21\times10^3$) due to the π-π^* and n-π^* transitions of the enone chromophore, respectively.[9] When CTAC micelles were introduced into the PGA_1 solution, the positive peak was shifted to shorter wavelengths (by about 3 nm) and the negative

Table 1. Kinetic parameters for micellar effect on isomerization of PGA at pH 11.2 and at 60 °C

Substrate			Micellar system			
	Partition[a] coefficient	k_o (min^{-1})		CMC ($\times 10^3$ M)	k_m (min^{-1})	K/N[b] (M^{-1})
PGA_1	80.8	0.038	CTAC	0.12	0.15	5000
			DTAC	1.7	0.12	590
			NaCS	0.14	0.034	—[c]
			NaLS	2.1	0.011	110
			Brij-35	0.75	0.12	220
PGA_2	69.4	0.044	CTAC		0.17	3900
			DTAC		0.14	470
			NaCS		0.041	—[c]
			NaLS		0.012	97
			Brij-35		0.14	190

a) Determined between chloroform and 0.1 M phosphate buffer of pH 6.0 at 25 °C. b) K: association constant of PGA-micelle complex, N: aggregation number of micelle. c) Could not be determined due to a small change in the rate constant.

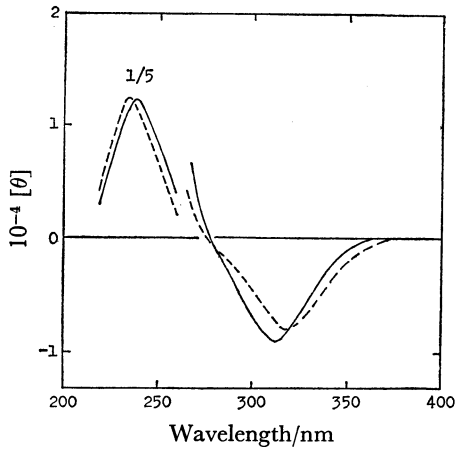


Fig. 2. The CD spectra of PGA_1 in the presence (-----) and absence (——) of CTAC (1.0×10^{-3} M) in 0.1 M phosphate buffer (pH=6.0, μ=0.2) at 25°.

peak was shifted to longer wavelengths (by about 8 nm). The effect of other surfactants on the CD spectra of PGA are similar to that of the PGA_1–CTAC system, for which the magnitude and direction of the spectral changes appears to be correlated with the association constants of PGA-micelle complexes. Similar spectra changes were also observed when PGA were dissolved in less polar solvents, such as ethanol-buffer and dioxane-buffer solutions. This type of spectral shift, the bathochromic shift of the π-π^* transition and the hypsochromic shift of the n-π^* transition with decreasing solvent polarity, is a well-known solvent effect in CD spectroscopy. Thus, the above results indicate that the chromophore of the PGA may be located in the hydrophobic circumstances of the micelles.

The rate enhancement observed for non-ionic micellar systems, however, cannot be interpretable soley on the basis of hydrophobic interactions. It was found that α- and β-cyclodextrins increase the isomerization rate with almost the same order of magnitude as dose Brij-35 in alkaline conditions,[10] for which the catalytic effects of cyclodextrins may be ascribed mainly to conformational changes of the substrate within the hydrophobic cavity of cyclodextrins and/or to alternations in the structure of the surrounding water.[11] An analogous situation is proposed for PGA-non-ionic micellar systems.

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