CHEMISTRY LETTERS, pp. 1109-1112, 1978. Published by the Chemical Society of Japan

PARTICIPATION OF CYCLODEXTRIN INCLUSION CATALYSIS IN PHOTOLYSIS OF CHLORPROMAZINE TO GIVE PROMAZINE IN AQUEOUS SOLUTION

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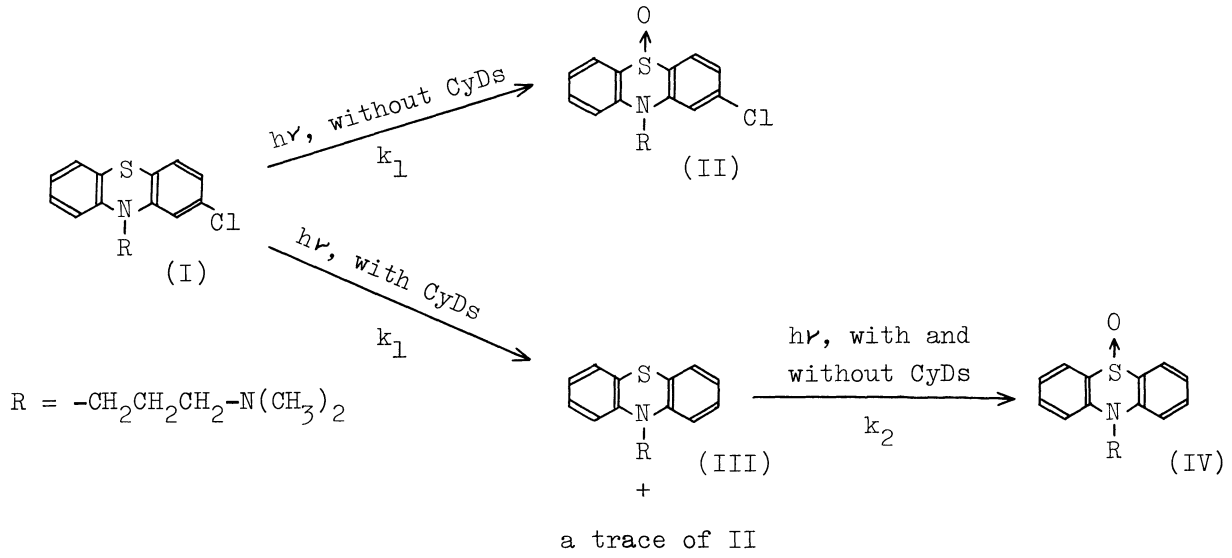
Photo-irradiation of chlorpromazine in the presence of cyclodextrins (CyDs) gave promazine in high yield in an aqueous solution. This dechlorination reaction and the proceeding photooxidation to give promazine sulfoxide were found to be largely dependent upon the cavity size of CyDs (β-CyD > γ-CyD > α-CyD), indicating a selective catalysis through formation of an inclusion complex.

Cyclodextrins (CyDs) are known to influence the rate of various kinds of chemical reactions, showing a feature of enzymatic reactions.[1] However, the catalytic behavior of CyDs in photolysis is little known.[2] We recently reported[3] the inclusion complex formation of tranquilizing phenothiazines with CyDs in aqueous solution, anticipating solubilization and stabilization of the drugs. Chlorpromazine (I), one of the most familiar tranquilizing drugs, is extremely sensitive to photo-irradiation, yielding mainly chlorpromazine sulfoxide (II).[4] In our preliminary photolysis of I, it was found that CyDs accelerate a dechlorination reaction to give a less biological active compound, promazine (III), in air-saturated aqueous solution at an acidic pH range. Thus, we now report the cavity size effect of CyDs (α-CyD, β-CyD, and γ-CyD) on this photochemical reaction.

A solution of I (5.0×10^{-4} M) or III (1.0×10^{-4} M) in the absence and in the presence of CyDs (5.0×10^{-3} M) in 0.1 M phosphate buffer (pH 2 ~ 7, ionic strength = 0.3) was irradiated with a 250 W Yōkō lamp (Toshiba DR 250/T Ⓛ, 25000 lux) through a Pyrex filter at 30 °C for 100 min. In the kinetic studies, I and III were quantitatively analysed by gas chromatography.

Figure 1 shows a typical gas chromatogram of photo-irradiation products of I in the presence of β-CyD, where a significant amount of III[5] was produced with a trace of II and promazine sulfoxide (IV).[6] Without CyDs, however, the main photolytic



Scheme I. Proposed scheme of the photolysis of I in the absence and in the presence of CyDs

product was found to be II and no production of III and IV was found under these reaction conditions. Figure 2 shows the time course of the photolysis of I in the absence and in the presence of CyDs. Although the effect of CyDs on the disappearance rate (k_1) of I was not remarkable, a little acceleration by the presence of α- and γ-CyDs and deceleration by β-CyD were noted as seen from Fig. 2A. On the other hand, the formation of III was largely depending upon the cavity size of CyDs (Fig. 2B). The yields of III in the absence and in the presence of CyDs at 30 min photo-irradiation of I are shown in Table I, where β-CyD system was found to give III in high yield in comparison with α- and γ-CyDs systems. This discrepancy may be ascribed to a high possibility of side reaction to form IV[7] (Scheme I), particularly for α- and γ-CyDs systems, as expected from their k_2 values in Table I. These results apparently indicate that either a smaller (α-CyD) or a larger (γ-CyD) cavity is rather unfavorable for cyclodextrin inclusion catalysis in the photolysis of I to give III. In fact, the stability constant (K_c) of I—β-CyD complex[8] is the largest among three CyDs's (see Table I).

An ESR study was conducted preliminarily to obtain an information on CyD-catalyzed photolysis of I. ESR spectra were taken by a Jeol JES-FE using a capillary cell. The experimental conditions were essentially the same as those described in Fig. 1, with exception of higher concentration of I (0.1 M). It was found that the photo-induced free radical production from I was significantly retarded by the presence of CyDs. Similar results were also observed in III-CyDs systems. Since the free radical is

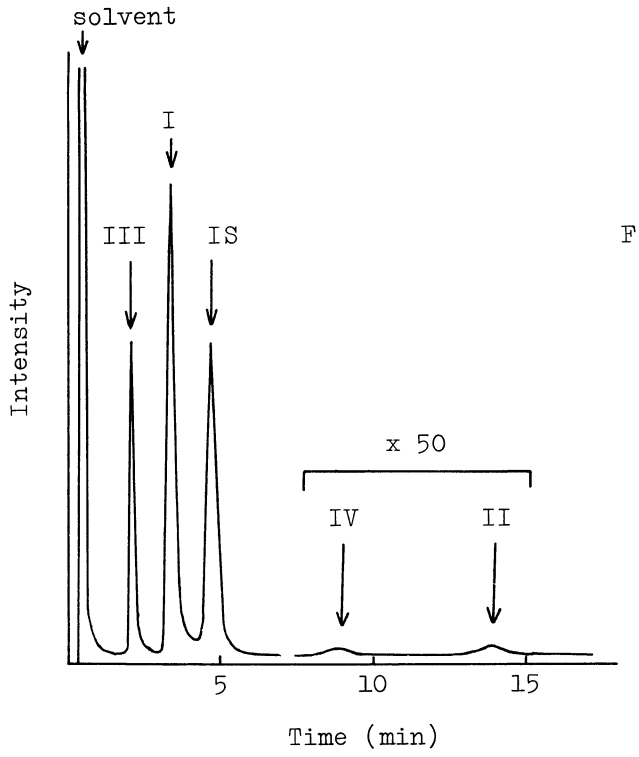


Fig. 1. Gas chromatogram of ether extract, after 100 min irradiation of I (5.0×10^{-3} M) + β-CyD (1.0×10^{-2} M) in 0.1 M phosphate buffer (pH 4.0, μ = 0.3) at 30 °C.

(column: Gas-chrom Q with silicon GE-SE-52 1 %, detector: FID, internal standard (IS): dinonyl phthalate, column temp.: 200 °C, detector temp.: 250 °C, injection: 3 μl)

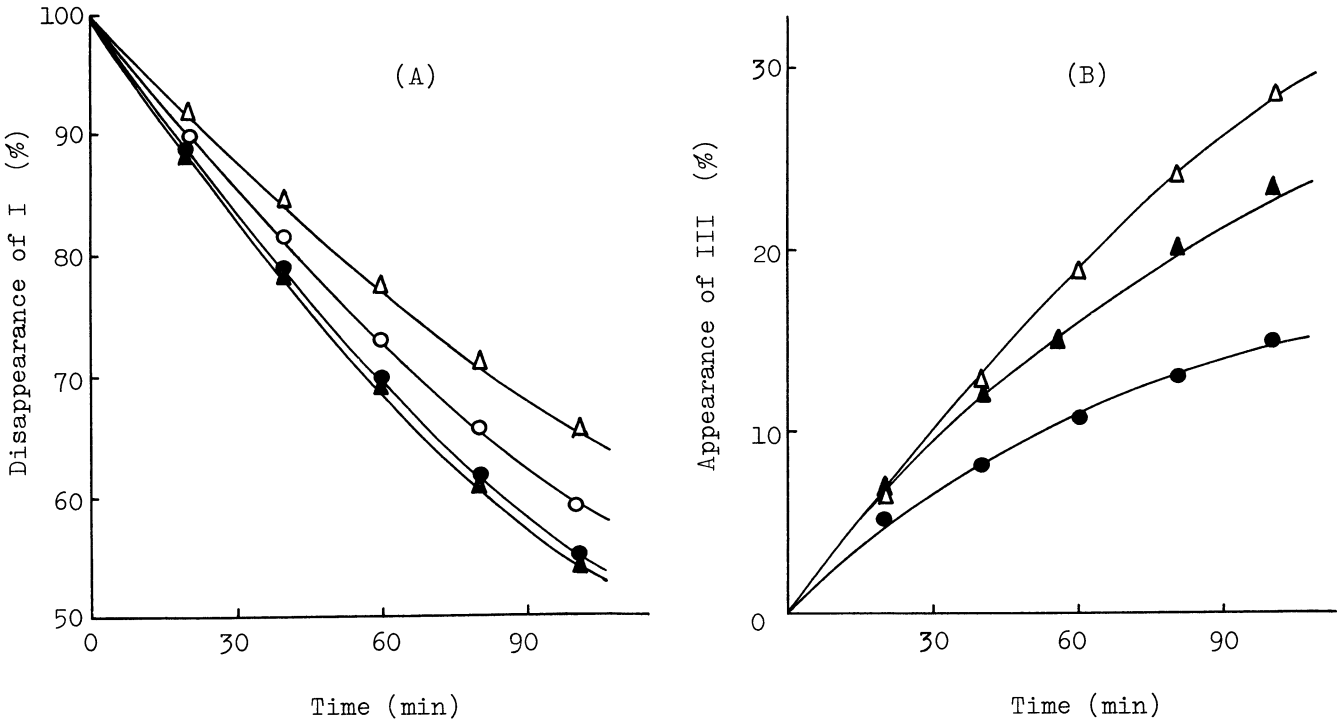


Fig. 2. Effects of CyDs (5.0×10^{-3} M) on the disappearance (A) of I and appearance (B) of III by photo-irradiation of I (5.0×10^{-4} M) in 0.1 M phosphate buffer (pH 4.0, μ = 0.3) at 30 °C.

Concentrations of I and III were monitored by gas chromatography.
o: without CyD, ●: with α-CyD, Δ: with β-CyD, ▲: with γ-CyD

Table I. Kinetic Data for Photolysis of I and III in the Absence and in the Presence of CyDs and Stability Constants of CyDs-I Complexes.

System	k_1[a] ($\times 10^3$ min^{-1})	k_2[b] ($\times 10^3$ min^{-1})	Yield of III[c] (%)	K_c[d] (M^{-1})
without CyDs	5.26	4.42	—	——
with α-CyD	6.02	4.29	41	200
with β-CyD	4.31	2.26	83	12000
with γ-CyD	6.11	3.26	58	1000

a) First order rate constant, calculated from the disappearance of I (starting material was I). b) First order rate constant, calculated from the disappearance of III (starting material was III). c) Based on the reacted I and estimated by gas chromatography, after 30 min photo-irradiation. d) Determined from UV absorption change (pH 7.0, 25 °C), according to the previous paper (ref. 3).

known to be generated during the course of photooxidation of phenothiazines,[9] the aforementioned facts may indicate that the CyDs complexes of I or III are particularly unsusceptible to the photooxidation reaction to give sulfoxides (II, IV). Thus, inhibition of the photooxidation of I or III by forming the cyclodextrin inclusion complex may be substantially responsible for the production of III in high yield.

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5) GC-Mass spectra were taken by a GC-MS-7000 (Shimadzu), and ascertained the identity of this photolytic product to an authentic sample.

6) Ascertained by TLC.

7) A produced amount of IV could not be quantitatively analysed by gas-chromatography because of the low sensitivity.

8) The present NMR study suggested that the chlor-substituted benzene ring of I was predominantly included within the cavity of β-CyD (ref. 3).

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(Received July 7, 1978)