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# Intramolecular Ring-Ring Stacking Interactions of New Bispsoralen Derivatives

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**Key words:** Bis($PsC_n$)PIP (n = 4, 6, 8), ring-ring stacking, hypochromic effect

## INTRODUCTION

Psoralens have been extensively utilized in the photochemotherapy of skin disorders such as psoriasis and vitiligo, and have recently been used in sterilization of human blood fractions for transfusion [1-3]. In particular, psoralens can inactivate the hepatitis B(HBV), hepatitis C(HCV), and human immunodeficiency virus(HIV) in blood [4-6]. Binding of psoralens to DNA is generally the consequence of two successive events. (1) intercalation into DNA between the base pairs and (2) photocycloaddition reaction of 3, 4-pyrone double bond and/or 4', 5'-furan double bond with 5, 6-double bond of thymine [7-9]. Bispsoralens have four photoreactive double bonds in a molecule as shown in Fig. 1 and consequently they have a high probability of photobinding to DNA. They can cross-link effectively not only just one double strand of DNA but also crosslink another adjacent double strand of DNA simultaneously leading to multi-strand cross-linked DNA. This will lead to very effective inactivation of DNA function. Photoaddition of psoralens to DNA is dependent on the reactivity of the chromophore and on the orientation of the interacting molecules. Bispsoralens linked by flexible polymethylene bridge can adopt folded conformations in solution and the position of the folded↔unfolded equilibrium is a measure of the intramolecular ring-ring stacking interaction. Most of the bispsoralens linked by polymethylene bridge have very low water solubility, limiting the utility of these molecules in clinics. Bispsoralens linked by polymethylene bridges containing piperazine are expected to give high water solubility and easily intercalate into DNA, and to have effective photobiological effects.

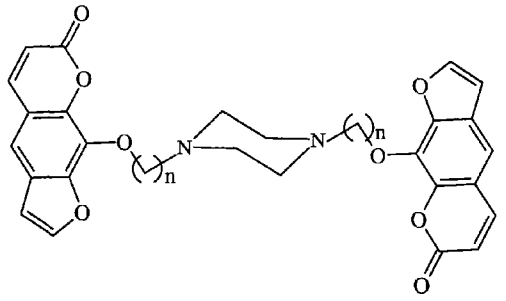

Figure 1. Chemical structure of Bis($PsC_n$)PIP, n = 4, 6, 8.

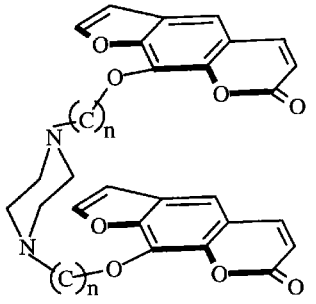

Figure 2. Intramolecular ring-ring stacking model of Bis($PsC_n$)PIP, n = 4, 6, 8.

We prepared 1, 4 - bis[n'-(8-psoralenoxy) alkyl] piperazine (Bis($PsC_n$)PIP, n = 4, 6, 8) having two psoralen moieties. We investigated the intramolecular ring-ring stacking interactions of these compounds.

## MATERIALS AND METHODS

*Materials and Instruments.* UV absorption spectra were recorded on a Shimadzu 3100S spectrophotometer at room temperature. 8-Methoxypsoralen (8-MOP) was obtained from Sigma Chemical Co. and purified by recrystallization from methanol. All the solvents were reagent grade or HPLC grade and purified according to the literature procedure [10]. Spectroscopic grade ethanol and methylene chloride were purchased from Merck and used as received. 1, 4 - Bis[(4'-(8-psoralenoxy)) butyl]piperazine (Bis($PsC_4$)PIP), 1,4 - bis[(6'-(8-psoralenoxy))hexyl] piperazine (Bis($PsC_6$)PIP) and 1, 4 - bis[(8'-(8-psoralenoxy))octyl] piperazine (Bis($PsC_8$)PIP) were synthesized by the reported procedures [11].

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*Methods.* Intramolecular ring-ring stacking interactions between aromatic moieties of Bis($PsC_n$)PIP has been investigated by measuring the hypochromic effect using UV absorption in the water-ethanol solution (95:5). Very low concentrations ($2.5\times 10^{-5}$ M) are employed in these measurements to avoid intermolecular contributions. The UV spectra were recorded in water-ethanol solution (95:5) at equimolar concentrations of the chromophores. The hypochromic effect can be quantitatively expressed by the percent hypochromism (%H).

$$\%H = [1-f\,(ps-linkage_n-ps) / 2f\,(8-mop)\,] \times 100$$

where f is the oscillator strength of the transition, i.e. a measure of the intensity of absorption,

$$f = 4.32\times 10^{-9} \int \varepsilon\lambda/\lambda^2 d\lambda$$

and $\varepsilon(\lambda)$ is the molar absorption coefficient. The percent hypochromism (%H) reflects the stacking of the two chromophores in the molecules and its value is generally considered as a measure of the interactions.

## RESULTS AND DISCUSSION

*Ring-ring stacking interaction*

Two psoralen molecules are linked by flexible methylene chains containing piperazine in Bis($PsC_n$)PIP. The compounds are in folded↔unfolded conformational equilibrium which will lead to variation in intercalation into DNA strands and piperazine moiety will give a good water solubility. The folded conformation will give higher intramolecular ring-ring stacking interactions which will give larger hypochromic effect. Consequently, the compounds with a large %H value will intercalate into the same strand of DNA, and this will inactivate DNA more thoroughly on UVA irradiation. The % H values, calculated for the whole spectrum (between 230 and 400 nm), are invariant with chain length as summarized in Table 1. The % H values were calculated for various regions of the spectrum of the three model compounds. For Bis($PsC_4$)PIP and Bis($PsC_6$)PIP, the magnitude of % H determined for the whole spectrum (230-400 nm) is similar suggesting about the same degree of stacking for the two compounds. However, smaller %H values were observed from the compound Bis($PsC_8$)PIP for the whole region reflecting a decrease of the folded conformation and less intramolecular ring-ring stacking interaction as the length of the bridging spacer is increased. As shown in Table 1, the degree of folding in Bis($PsC_8$)PIP is lower than those of Bis($PsC_4$)PIP and Bis($PsC_6$)PIP, indicating that the intramolecular stacking decreases as the length of the bridging chain is elongated. The trend is typically conspicuous in 300-400 nm region. The % H values of Bis($PsC_4$)PIP, Bis($PsC_6$)PIP and Bis($PsC_8$)PIP in this region which is the most important region in PUVA therapy, are 14.1, 14.6 and 3.9.

Table I. Percent hypochromism values (%H) were calculated for models (Bis($PsC_n$)PIP) in various wavelength regions. UV spectra were measured in $H_2O$-EtOH (95:5), 20°C.

| λ (nm) | Bis($PsC_4$)PIP | Bis($PsC_6$)PIP | Bis($PsC_8$)PIP |
|---|---|---|---|
| 230-400 | 13.8 | 15.6 | 8.7 |
| 260-400 | 15.2 | 15.4 | 3.7 |
| 280-400 | 15.0 | 15.6 | 6.2 |
| 300-400 | 14.1 | 14.6 | 3.9 |
| 235-280 | 13.9 | 16.3 | 10.8 |

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