Photo-induced DNA cleavage reaction characteristics of propargylic sulfones possessing an anthraquinone chromophore

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ABSTRACT
Propargylic sulfones (PS) are known as pH dependent DNA cleaver. DNA cleavage by PS was considered to proceed by alkylation of G base to allenic sulfones formed from PS in basic condition. We designed PS possessing naphthalene and anthraquinone (AQ) unit and investigated DNA cleavage characteristics. Although these compounds showed high intercalating abilities, this high intercalating ability did not lead to DNA cleaving activity. This result indicates that spatial arrangement of activated allene against guanine base is very important in DNA cleavage by PS. In addition, UV-irradiation to PS possessing AQ unit leads to efficient DNA cleavage at 5'-G of GG sequence. This cleavage pattern exhibited typical cleavage of one-electron oxidation of B-form DNA. Therefore, this result suggests that PS possessing AQ unit cleave DNA by both the alkylation mechanism and the photooxidation mechanism.

RESULTS AND DISCUSSION
DNA binding ability.
Initially, binding constant of propargylic sulfones (PS) to Salmon Sperm DNA was determined. As shown in Table 1, PS 3 shows about 2 and 1.2-fold higher intercalating ability than 1 and 2, respectively. These results indicate that introduction of an intercalating unit to propargylic sulfones raises their intercalating ability.

Table 1. Structures and DNA binding constants K⁺ (in units of 10⁴ M⁻¹) of propargylic sulfones 1-3.

<table>
<thead>
<tr>
<th>Ar</th>
<th>R = H</th>
<th>R = O₃SAr</th>
<th>K⁺ (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹</td>
<td>1</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>²</td>
<td>2: 3.2</td>
<td></td>
<td>3: 3.7</td>
</tr>
</tbody>
</table>

DNA cleaving activity.
We next examined DNA cleavage by PS. As shown in Fig-
ure 1, DNA cleavage by PS 3 was less efficient than that of 2 without UV-irradiation. This result was opposed to the order of DNA binding ability as measured by $K'$ shown in Table 1. The $K'$ value of AQ and naphthalene were $11.3 \times 10^4$ M$^{-1}$ and $5.2 \times 10^4$ M$^{-1}$, respectively. Therefore, 3 would intercalate DNA mainly from AQ unit. As shown in Figure 2, when AQ unit of 3 intercalate to DNA, activated allene is far from nucleobases. On the other hand, the intercalation from 2-naphthalene unit guide allenic site of 3 to appropriate position for alkylation of nucleobase. In accord with this prediction, 3 showed less efficiency in DNA cleavage than 2 which intercalates DNA exclusively from naphthalene unit. This result indicates that appropriate distance between activated allenic site and nucleobase is important for the DNA cleavage by the nucleobase alkylation mechanism.

![Figure 1](image1.png)

**Figure 1.** The scanning densitometry results of DNA cleavage by PS 2 and 3 in 20% DMSO containing TAE buffer (pH 8.5).

We next investigated the DNA cleavage by 3 with UV-irradiation and incubation. As predicted, 3 showed more efficient DNA cleavage with UV-irradiation than without UV-irradiation. This result indicates that combination of alkylation with photoinduced oxidation results in more efficient DNA cleavage. The quantum yield for DNA cleavage by 3 was evaluated as $2.2 \times 10^{-3}$.

**Analyses of DNA cleaving site.**

The base selectivity of the DNA cleavage by PS 3 was further investigated. As shown in Figure 3, 3 caused DNA cleavage at every guanine bases after the incubation at 37 °C. This result supports the mechanism by which 3 causes DNA cleavage via the alkylation at guanine bases. Moreover, enhancement of DNA cleavage by 3 of 5'-G of GG steps was observed under UV-irradiation followed by incubation. It is well known that 5'-G of 5'-GG-3' is a sink in hole migration through DNA, i.e. an electron-loss center created in B-form DNA would end up predominantly on 5'-G of GG steps. Therefore, these results suggest that 3 cleaves DNA by both alkylation and one-electron oxidation under UV-irradiation followed by incubation.

![Figure 3](image3.png)

**Figure 3.** DNA cleavage by PS 3. The arrows indicate the relative frequencies of DNA cleavage after incubation (solid arrows) or after UV-irradiation followed by incubation (open arrows).

**REFERENCES**